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Information provision and patient reported outcomes in cancer survivors

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INFORMATION PROVISION
AND PATIENT REPORTED OUTCOMES IN CANCER SURVIVORS:
WITH A SPECIAL FOCUS ON THYROID CANCER



Olga Husson

**Information provision and patient reported
outcomes in cancer survivors:**
with a special focus on thyroid cancer

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CHAPTER 1

General introduction



Growing number of cancer survivors

With the ongoing improvements in early detection and treatment of cancer along with the ageing of the population, the number of cancer survivors is rapidly increasing in the Western world. In 2010, there were about 600,000 cancer survivors in The Netherlands, expected to increase to 915,000 in 2020 ¹. Cancer has increasingly been referred to as a chronic disease since the majority (59%) of the patients survive relatively long-term (>5 years after diagnosis) ².

Definition of a ‘cancer survivor’

The concept of cancer survivorship and the population which the definition covers has been widely discussed and interpreted over the last decades ³. Since the 1960’s, when treatments started to improve, health care practitioners defined “cancer survivors” as those persons who had survived at least 5 years since initial diagnosis or treatment ⁴. The number of cancer survivors increased further in the 1970’s and 1980’s and the US National Coalition for Cancer Survivorship (NCCS), a ‘survivor-led advocacy organization’ was founded. One of the founders of the NCCS, Fitzhugh Mullan, describes his personal experience as follows (1985): *‘Actuarial and population-based figures give us survival estimates for various cancers, but those figures do not speak to the individual patient, whose experience is unique and not determined or described by aggregate data. Many patients are “cured” long before they pass the five-year mark, and others go well beyond the five-year point with overt or covert disease that removes them from the ranks of “cured”, no matter how well they feel. Survival is a much more useful concept, because it is a generic idea that applies to everyone diagnosed as having cancer, regardless of the course of illness. Survival, in fact, begins at the point of diagnosis, because that is the time when patients are forced to confront their own mortality and begin to make adjustments that will be part of their immediate, and to some extent, long-term future’* ⁵.

The NCCS therefore defines a person diagnosed with cancer a survivor from the moment of diagnosis through the balance of his or her life ⁶. This definition was also used by the Institute of Medicine (IOM) in their report “Lost in transition” ⁴ and was adapted by The National Cancer Institute’s Office of Cancer Survivorship. The latter however also included family members, friends, and caregivers since they are also impacted by the survivorship experience ⁴. In this thesis we use the definition of the NCCS and IOM, focusing only on the cancer survivor, and not including relatives or caregivers. This definition shows that potentially anyone with a diagnosis of cancer can be a survivor. This definition also raises the awareness of the need to consider issues of survival from the start of cancer treatment ⁴.

Why study the fate of (long-term) cancer survivors?

Scientific evaluations of new treatments and care protocols for cancer patients are traditionally based on biological outcomes, specifically disease-free and overall or relative survival ⁷. Although improving survival is an important issue in cancer treatment, evaluating (long-term) sequelae of treatment will finally determine the functional effectiveness of the treatment ⁸. Health-related quality of life (HRQoL) and other patient reported outcomes (PROs) are more and more recognized to be of importance ⁹, especially since many new treatments have only a marginal impact on survival rates, and many survivors face continuing physical and psychosocial problems after completion of primary treatment ⁷. Achieving and maintaining optimal well-being must be an important objective of current cancer treatment, cancer rehabilitation and aftercare.

In the past decade a growing number of studies has documented the high prevalence of short-term effects (e.g. hair loss, pain, nausea and vomiting, anemia), long-term effects (e.g. fatigue, pain, memory problems and sexual dysfunction) and late effects (e.g. second malignancies, cardiovascular disease and osteoporosis) of cancer treatment ^{10, 11}. Furthermore, research shows that many survivors experience a decline in HRQoL, fear of recurrence, high levels of anxiety and depression, employment, insurance and financial problems and relationship difficulties ^{10, 12, 13}. Due to these research findings concerns about long-term physical, psychosocial and economic effects of cancer and its treatment are increasingly being recognized and new therapies not only focus at maximizing cure but also at minimizing long-term effects. Up to now, most of these survivorship studies focused on survivors of common types of cancer like breast, colorectal and prostate cancer.

Thyroid cancer survivors: an underexposed group

Although the knowledge about cancer survivorship has grown in the past decade, survivors of rare tumours, like thyroid cancer, so far received little attention in the cancer survivorship literature. Each year 500-600 patients are diagnosed with thyroid cancer in The Netherlands ². Due to the increasing incidence and good prognosis of papillary and follicular thyroid cancer (exceeding >90% 5-year survival) ¹⁴ the number of thyroid cancer survivors is increasing rapidly. In 2000, 3800 people survived thyroid cancer diagnosed in the past 20 years vs. 5500 in 2010, an increase of 45% ¹. Treatment of thyroid cancer involves surgery, predominantly (near-) total thyroidectomy with or without lymphadenectomy, followed by radioiodine (iodine-131) therapy to ablate the remaining thyroid tissue. Depending on type and size of the tumour hemithyroidectomy could suffice. The removal of the whole thyroid gland is accompanied by a lifelong dependence on supplement therapy with exogenous thyroid hormone (levothyroxine), in the first years with dosing regimens suppressing thyroid stimulating hormone (TSH) production ^{15, 16}. Despite the efficacy of these primary treatments, 15-35% of the patients develop a locoregional recurrence or

distant metastases, even decades later ¹⁷. Therefore, intensive long-term periodical follow-up is necessary. Given the longevity of thyroid cancer survivors and the radical surgery and aggressive postoperative radioiodine treatment accompanied by a lifelong dependence on exogenous thyroid hormone, possible (long-term) physical and psychosocial problems are of considerable concern. However, the number of studies focusing on quality of life of (long-term) thyroid cancer survivors is limited.

Cancer survivorship care: Information provision

Survivorship care includes four components: (1) prevention and detection of new cancers and recurrent cancer; (2) surveillance for cancer spread, recurrence, or second cancers; (3) intervention for consequences of cancer and its treatment; and (4) coordination between specialists and primary care providers to ensure that all of the survivor's health needs are met ⁴. An essential factor of supportive cancer care across all four components is the provision of information. The goals of information provision are to assist patients in making treatment decisions, prepare patients for their treatment, increase treatment adherence and abilities to cope with the illness as well as to promote recovery ^{18, 19}. Until the 1980s most doctors disclosed only selected information about cancer. With the introduction of the concept of cancer survivorship in 1986, more attention has been paid to the information needs of cancer patients and their right to be fully informed, particularly in the Western world ²⁰.

Previous research showed that information needs are prevalent among cancer survivors and the majority (>80%) of cancer survivors even want to be fully informed ²¹⁻²³. The nature of information needs is associated with the stage across the cancer continuum. During diagnosis and treatment the most prominent information needs are information about disease stage, treatment options and side-effects of treatment. Post-treatment, patients report a continued need for treatment related information and also information about rehabilitation is important ²². Other studies showed that socio-demographic and clinical factors like age, sex, disease stage, marital status, educational level and ethnicity, may also influence information needs ¹⁸. For example, younger age has been associated with more information needs and female survivors have reported more psychosocial information needs, while males have reported more information needs related to treatment ²⁴. Furthermore, information needs might also vary as a function of adjustment to cancer and it is suggested that personality traits may inhibit or assist information seeking behavior ^{25, 26}.

A systematic review showed that 6–93% of the cancer survivors report adequate information provision as an unmet need throughout the cancer continuum ²⁷. Especially the information needs of cancer survivors post-treatment are unmet ²². This may be because health

care providers do not have enough time and resources to inform patients appropriately. Furthermore, patients may have difficulty understanding the often complex information or have problems with processing the potentially upsetting information²⁵. In addition, there is a discrepancy between the actual information needs of cancer patients and the perception of health care providers about the needs of cancer patients²⁸. It is important that this discrepancy disappears, since the provision of tailored information, that is congruent with patients' needs, is an important determinant for patient satisfaction²⁹. Additionally, unmet information needs and dissatisfaction have been linked to negative PROs like increased emotional distress (anxiety and depression) and HRQoL^{30,31}. However, the number of studies that investigated these associations is limited and inconclusive because of methodological flaws such as cross-sectional designs and use of self-developed and not yet validated questionnaires or single questions to assess information provision.

AIMS AND ORGANIZATION OF THIS THESIS

The current thesis can be subdivided into two parts. Part I addresses the perceived level of, and satisfaction with, information received by cancer survivors in different stages of their disease and how this is related to PROs like HRQoL, distress (anxiety and depression) and illness perception. Part II addresses the (long-term) health-related quality of life of thyroid cancer survivors.

Part I - Information provision and patient reported outcomes

In the past decade, the role of information provision in (supportive) cancer care has been acknowledged. Throughout this thesis information provision is defined as all cancer-related information provided by the health care provider in oral, written or other form. Part I of this thesis is guided by the conceptual model presented in Figure 1.

Investigating the current state of information provision and degree of satisfaction with information provision of cancer survivors is necessary to determine whether the information provision is sufficient, or whether improvements are necessary (centre of conceptual model). Therefore the aim of **Chapter 2** was to assess the perceived level of and satisfaction with information received by melanoma cancer survivors with an internationally validated questionnaire³². Furthermore, possible associations between clinical and socio-demographic characteristics and the perceived level of and satisfaction with received information were explored (left part of conceptual model).

Furthermore individual differences in personality might be related to the perception of received information. Recently, a large amount of studies focused on the effects of Type D personality on clinical and psychological outcomes in different patient populations³³⁻³⁵. A distressed personality (Type D) is defined by the combination of two personality traits;

the tendency to experience negative emotions (negative affectivity) and to inhibit self-expression in social interaction (social inhibition)³⁶. The combination of the two personality traits possibly makes Type D patients vulnerable for inadequate information provision, since they probably experience more negative emotions associated with medical information and will probably not ask for further information if their needs are not met. Therefore, differences in the perceived level of, and satisfaction with, information received by Type D and non-Type D cancer survivors of diverse cancer types were described in **Chapter 3**.

Next to the clinical, socio-demographic and psychological factors that might influence the perceived level of and satisfaction with the received information, some PROs might have a bidirectional relationship with information provision (right part of conceptual model). Several studies have investigated the relationship between information provision and HRQoL, anxiety and depression, **Chapter 4** gives an overview of these studies.

Patients respond to their illness by forming cognitive and emotional representations of the illness that lead to coping responses³⁷. These illness perceptions are a major determinant of HRQoL³⁸ and are possibly associated with information provision. Therefore, the aim of **Chapter 5** was to examine the association between illness perceptions and information provision among a diverse group of 3080 cancer survivors.

The studies included in our systematic review focused on cancer survivors without advanced disease. Patients with metastasized cancer might have different information needs and perceptions compared to patients with non-metastatic cancer. The objective of **Chapter 6** was to measure the perceived level of, and satisfaction with, information received by patients with metastatic (stage IV) colorectal cancer as compared with patients with non-metastatic (stage I,II,III) colorectal cancer. Furthermore, associations of information provision with HRQoL, anxiety and depression, and illness perceptions were examined for patients with metastatic disease only.

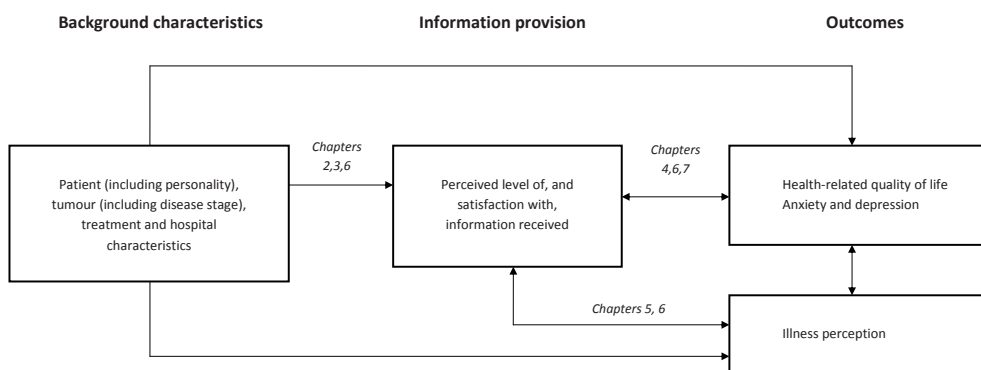


Figure 1: Conceptual model of information provision and patient reported outcomes. The numbers indicate the chapter numbers of this thesis where the relationship is discussed.

Most studies described in the systematic review (*Chapter 4*) had a cross-sectional design and determination of causal associations was therefore difficult. The relationship between information provision and prospectively assessed HRQoL, anxiety and depression among a large group of lymphoma and multiple myeloma survivors was examined in *Chapter 7*.

Part II - Thyroid cancer survivors: an understudied group

The first aim of Part II of this thesis was to assess trends in incidence, mortality, and survival of thyroid cancer in The Netherlands between 1989 and 2009 (*Chapter 8*). This chapter shows that the prevalence of thyroid cancer is rising. Given the longevity of thyroid cancer survivors and the radical surgery and aggressive postoperative radioiodine treatment accompanied by a lifelong dependence on supplemental exogenous thyroid hormone, possible (long-term) physical and psychosocial problems are of considerable concern. In *Chapter 9* the existing literature on HRQoL of thyroid cancer survivors was systematically reviewed. The studies included in the review showed contradictory results and there were several methodological issues that impede drawing strong conclusions on the HRQoL of (long-term) thyroid cancer survivors. The main problem was the lack of a valid, thyroid cancer specific instrument to assess HRQoL. Most studies only used a general HRQoL questionnaire, which cannot capture the specific complaints associated with thyroid cancer and its treatment. The development of a thyroid cancer specific HRQoL questionnaire applicable in combination with the core questionnaire of the European Organisation for Research and Treatment of Cancer (EORTC QLQ-C30)³⁹ was described in *Chapter 10*.

Since long-term thyroid cancer survivorship studies were lacking, the aim of *Chapter 11* was to assess (thyroid cancer specific) HRQoL among long-term thyroid cancer survivors and to compare this with the HRQoL of an age- and sex-matched normative population. The second objective was to investigate which clinical and socio-demographic characteristics and thyroid cancer specific problems were associated with HRQoL.

Fatigue is a common problem among patients with (subclinical) hyperthyroidism⁴⁰, as is the case for thyroid cancer survivors with suppressing doses of levothyroxine in the first years after surgery. It can therefore be expected that short-term thyroid cancer survivors (<5 years since diagnosis) report higher levels of fatigue compared to a normative population or long-term thyroid cancer survivors (≥5 years since diagnosis) who have returned to a euthyroid state. Up to now, no study has focused on the level of fatigue among thyroid cancer survivors. Therefore, the aim of *Chapter 12* was to obtain insight into the prevalence of fatigue among short-term (<5 years) and long-term (≥5 years) thyroid cancer survivors, by comparing a sample of thyroid cancer survivors with an age- and sex-matched normative population. Furthermore, associations between clinical and socio-demographic characteristics and thyroid cancer specific problems with fatigue were assessed.

In **Chapter 13** the main findings of this thesis will be discussed and implications for future research and clinical practice will be outlined.

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CHAPTER 2

Melanoma survivors are dissatisfied with perceived information about their diagnosis, treatment and follow-up care

O. Husson, C. Holterhues, F. Mols, T. Nijsten, L.V. van de Poll-Franse



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MADAM, The incidence of melanoma is rapidly rising which can lead to an increasing burden for health care providers ¹. Information provision is one of the most important aspects of supportive cancer care. Providing information that is congruent with patients' needs may lead to lower levels of distress, better quality of life, improved patient satisfaction and sense of control ^{2,3}. More disease knowledge can result in informed decision making and can have positive effects on treatment- and follow-up adherence leading to reduced follow-up visits ¹. However, one of the most frequently reported unmet needs by cancer patients is information disclosure ⁴. There is a discrepancy between the actual information needs of cancer patients and the perception of health care providers about the needs of cancer patients ⁵. Health care providers are often still reluctant to give the full amount of information about cancer and its treatment. Melanoma patients would appreciate especially more information concerning their diagnosis, treatment and skin condition ⁶.

We conducted a cross-sectional study to measure the perceived level of, and satisfaction with, information received by melanoma patients ⁷. Patients diagnosed with melanoma between January 1st 1998 and August 1st 2007 from three regional hospitals were selected. Melanoma was defined using the ICD-O codes: C44.0-C44.9 with morphology 8720-8790. Medical specialists sent their (former) patients a letter to inform them about the study and a questionnaire. The EORTC-QLQ-INFO26 questionnaire was used to evaluate the information received by melanoma patients ⁸.

Of the 699 melanoma survivors, 562 (80.4%) returned a completed questionnaire. There were no demographic or clinical differences between respondents and non-respondents. Demographics and clinical characteristics of participating patients are presented in Table 1. A large percentage of patients indicated the absence of information about different aspects of melanoma, treatment and aftercare (Table 2).

In multivariate linear regression analysis, none of the patient characteristics were significantly associated with perceived information provision about the *disease*. More information about *medical tests* was associated with shorter time since diagnosis ($\beta = -0.10$; $p < 0.05$) and a higher stage melanoma ($\beta = 0.19$; $p < 0.01$). More perceived information provision about *treatment* was significantly independently associated with younger age ($\beta = -0.15$; $p < 0.05$), higher stage of disease ($\beta = 0.20$; $p < 0.01$) and higher educational level ($\beta = -0.10$; $p < 0.05$). Logistic regression analysis showed that satisfaction with information was independently associated with hospital of treatment (odds ratio, OR = 0.49 (95% CI 0.32-0.76), $p < 0.01$), high educational level (OR = 0.63 (95% CI 0.41-0.99), $p < 0.05$) and less frequent use of the internet for additional information (OR = 0.60 (95% CI 0.39-0.92), $p < 0.05$). Patients with a higher disease stage are more likely to undergo more medical tests and/or treatments due to the increased risk of recurrence and metastasis. Therefore these patients might get more attention and information from their health care providers compared to patients with stage I melanoma. Also, the majority of melanoma patients receive most information immediately after diagnosis. After the completion of treatment the contacts of the patients with their doctor will diminish ³, while the information need of the melanoma survivor may still exist. Patients diagnosed and treated shortly before the completion of the questionnaire, might have a clearer picture of the information they received and therefore reported to have received more information.

Table 1: Demographics and clinical characteristics of participating patients (N = 562)

	Total N (%)
Age at time of survey (mean(SD))	57.2 (13.6)
Gender	
Male	212 (38%)
Female	350 (62%)
Years since incidence (mean (SD))	4.6 (2.6)
Stage at diagnosis	
I	400 (71%)
II	108 (19%)
III	42 (8%)
IV	-
Breslow	
≤ 1.0 mm	275 (49%)
1.01-2.0 mm	149 (27%)
2.01-4.0 mm	100 (18%)
>4.0 mm	32 (6%)
Treatment	
Surgery	556 (99%)
Sentinal Node	113 (20%)
Lymphadenectomy	27 (5%)
Radiotherapy	3 (0.5%)
Systemic therapy	3 (0.5%)
Other	29 (5%)
Comorbidity	
None	190 (35%)
One	174 (32%)
Two or more	174 (32%)
Hospital	
Hospital A	168 (30%)
Hospital B	255 (45%)
Hospital C	139 (25%)
Marital status	
Married	416 (74%)
Never married	55 (10%)
Divorced/widowed	89 (16%)
Education level	
Higher education	161 (29%)
Intermediate education	242 (43%)
Secondary school	103 (19%)

Table 1: Demographics and clinical characteristics of participating patients (N = 562) (*Continued*)

	Total N (%)
Primary school	52 (9%)
Current occupation	
Employed	248 (44%)
Unemployed	311 (56%)
Socioeconomic status	
Low	80 (15%)
Intermediate	220 (40%)
High	237 (44%)
Institutionalized	6 (1%)
Follow-up care	
General practitioner	11 (2%)
Dermatologist	452 (81%)
Surgeon	138 (25%)
Oncologist/internist	48 (9%)
Other	12 (2%)

Younger and higher educated melanoma patients are more likely actively involved in decision-making processes and ask more questions. Older patients are reported to be less interested in detailed information and leave the provision of details up to the doctor ⁹. Likewise, doctors can be prejudiced against older patients. Furthermore, older and less educated patients may have more difficulties processing and remembering information they receive and may compensate for their reduced cognitive capacity by asking fewer questions to their specialist ⁹.

The observed variation in information satisfaction levels between patients treated in different hospitals can be explained by the variation in patient-centred information giving, which is strongly related to information recall and understanding. Our finding that only 25% of the melanoma survivors wanted more information could be explained by the increasing internet use of melanoma patients ¹⁰. When patients are not satisfied with the information received from their health care provider, they will search for additional information on the internet.

Health care providers often have limited time and resources to provide the information that melanoma patients require. With growing evidence that well-informed patients are more satisfied with their care, and do better clinically, efforts are needed to improve the information provision to melanoma patients. Exploration of the patients personal information needs must lead to a more patient-tailored approach of informing melanoma patients. A good opportunity would be the implementation of a survivorship care plan, which aims at providing a cancer survivor with a summary of their course of treatment, management of late effects, and strategies for health promotion.

Table 2: Perceived information provision characteristics (N (%))

	Received no information	Received a little information	Received quite somewhat information	Received a lot of information
Disease				
Diagnosis	47 (9%)	309 (56%)	154 (28%)	41 (7%)
Spread disease	104 (19%)	271 (49%)	135 (25%)	37 (7%)
Cause disease	203 (37%)	226 (41%)	103 (19%)	17 (3%)
Under control	76 (14%)	258 (47%)	164 (30%)	48 (9%)
Medical tests				
Purpose test	134 (25%)	220 (41%)	157 (29%)	29 (5%)
Course test	125 (23%)	237 (44%)	144 (27%)	32 (6%)
Results test	74 (14%)	237 (44%)	188 (35%)	38 (7%)
Treatment				
Medical treatment	201 (38%)	162 (30%)	137 (26%)	30 (6%)
Non-medical treatment	496 (94%)	26 (5%)	5 (1%)	2 (0%)
Expected result	182 (34%)	202 (38%)	122 (23%)	25 (5%)
Side effects	333 (62%)	131 (25%)	56 (10%)	14 (3%)
Expected results on disease symptoms	288 (54%)	163 (31%)	65 (12%)	14 (3%)
Expected results on social life	423 (80%)	84 (16%)	18 (3%)	7 (1%)
Expected results on sexual life	487 (92%)	32 (6%)	6 (1%)	5 (1%)
Other services				
Additional help	484 (92%)	36 (7%)	6 (1%)	2 (0%)
Rehabilitation	481 (91%)	28 (5%)	14 (3%)	4 (1%)
Cope with cancer at home	441 (84%)	68 (13%)	16 (3%)	2 (0%)
Psychological assistance	492 (94%)	29 (5%)	3 (1%)	2 (0%)
Single items				
Different care locations	472 (91%)	38 (7%)	9 (2%)	3 (0%)
Things to do to get better	399 (76%)	92 (18%)	25 (5%)	7 (1%)
	Not satisfied	A little satisfied	Quite satisfied	Satisfied
Satisfaction with information	72 (13%)	259 (48%)	164 (30%)	46 (9%)
	Not useful	A little useful	Quite useful	Very useful
Usefulness information	43 (8%)	224 (43%)	194 (38%)	57 (11%)
	Yes	No		
Received written information	279 (52%)	259 (48%)		
Received information on video or cd-rom	4 (1%)	538 (99%)		
Wanted more information	135 (25%)	402 (75%)		
Wanted less information	10 (2%)	518 (98%)		

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CHAPTER 3

Satisfaction with information provision in cancer survivors and the moderating effect of Type D personality

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Revision submitted

ABSTRACT

Objective: Optimal information provision is important in cancer survivorship, but satisfaction with this provision may depend upon individual differences in personality. We examined the effect of personality traits negative affectivity and social inhibition and their combined effect (Type D personality) on satisfaction with information received.

Methods: Four population-based, cross-sectional surveys were conducted through the Eindhoven Cancer Registry (ECR). All individuals diagnosed with lymphoma, multiple myeloma, endometrial cancer or colorectal cancer (1998-2008) as registered in the ECR were eligible for participation. In total, 4446 patients, received questionnaires including the EORTC QLQ-INFO25 and the Type D personality scale (DS14); 69% responded (n=3080).

Results: Nineteen percent of patients (n=572) had a Type D personality. On the information provision subscales of the EORTC QLQ-INFO25 (scale 0-100), the perceived receipt of disease specific (mean 46 vs. 51), medical test (56 vs. 63) and treatment information (37 vs. 42) was significantly lower for Type D patients compared to non-Type Ds (all P s<0.01). Type D cancer patients were less satisfied with the received information (49 vs. 58; p <0.01) and found the received information less useful (55 vs. 61; p <0.01) compared to non-Type Ds. Multivariate linear regression analyses showed that Type D personality was independently associated with information about the disease (Beta=-0.09), medical tests (Beta=-0.12) and treatment (Beta=-0.08) and with satisfaction with information received (Odds ratio=0.54; 95%CI=0.44-0.66; all P s<0.01).

Conclusions: This study showed that patients with a Type D personality perceived to receive less information and reported less satisfaction with the amount of received information as compared to non-Type D patients.

INTRODUCTION

Providing cancer patients with appropriate information is one of the most important aspects of cancer care across the whole cancer continuum. Information provision is defined as all cancer-related information provided by the health care provider/nurse in oral, written or other form¹. Adequate information provision can result in informed decision making, better treatment adherence, better health-related quality of life (HRQoL), lower levels of distress, improved satisfaction with care and sense of control^{1,2}. However, one of the most frequently reported unmet needs by cancer patients in all phases of the disease is information provision³. This indicates that health care providers and patients differ in their perceptions of information needs⁴ and differences between health care providers in communication skills⁵. Information provision can be difficult since medical information is often complex and sometimes emotionally charged (e.g. likelihood of survival)⁶. The majority of cancer patients want as much information as possible about their disease, treatment and rehabilitation⁷. However, information needs vary by sex, age, cultural background, time since diagnosis, educational level, disease stage and as a function of adjustment to cancer^{6,8}.

There also may exist substantial differences in the information needs of cancer patients as a function of underlying individual differences in personality. It has been suggested that personality characteristics may inhibit or assist information seeking⁹. Studies have shown that personality characteristics such as high internal locus of control, self-esteem and self-efficacy are shown to contribute positively to information seeking¹⁰⁻¹², while nervousness formed an obstacle for seeking information for 20% of cancer patients¹³. Information seeking is frequently described as a coping mechanism, where patients with a monitoring style tend to require more information and patients with a blunting style feel better with less information¹⁴. However, little research to date has focused on the area of personality and information provision in cancer survivorship.

Recently, a large amount of studies focused on the effects of Type D personality on clinical and psychological outcomes in different patient populations¹⁵⁻¹⁷. A distressed personality (Type D) is defined by the combination of two personality traits; the tendency to experience negative emotions (negative affectivity) and to inhibit self-expression in social interaction (social inhibition)¹⁸. Studies showed that cancer patients with a Type D personality experience a lower quality of life and mental health status¹⁹, report higher rates of comorbid conditions and to report to feel more bothered by these conditions²⁰. Also, patients with a Type D personality had more negative perceptions about their illness, were more concerned about their illness and felt that their disease more often influenced them emotionally²¹. A possible explanation for these negative illness perceptions is that there might be a difference

in the perceived receipt of information between cancer patients with and without a Type D personality, however research on this topic is lacking.-

Therefore, the aim of this study was to evaluate differences in the perceived level of, and satisfaction with, information received by Type D and non-Type D cancer patients. We hypothesized that Type D patients would indicate to receive less information and to be less satisfied with it as compared to non-Type D patients, since they probably experience more negative emotions (for example anxiety, sadness, anger, depression, guilt) associated with medical information (negative affectivity) and will probably not ask for further information if their needs are not met (social inhibition).

METHODS

Setting and Participants

For this study, data from four large population-based cross-sectional surveys on patients of endometrial cancer, colorectal cancer, lymphoma and multiple myeloma was used ²²⁻²⁶. These surveys were set up between 2008 and 2009 with the goal to evaluate various patient-reported outcomes among cancer patients. Data collection was done within PROFILES (Patient Reported Outcomes Following Initial treatment and Long term Evaluation of Survivorship). PROFILES is a registry for the study of the physical and psychosocial impact of cancer and its treatment from a dynamic, growing population-based cohort of both short- and long-term cancer survivors ²². PROFILES contains a large web-based component and is linked directly to clinical data from the Eindhoven Cancer Registry (ECR), which compiles data of all individuals newly diagnosed with cancer in the southern part of the Netherlands, an area with 10 hospitals serving 2.3 million inhabitants ²⁷. Data from the PROFILES registry will be available for non-commercial scientific research, subject to study question, privacy and confidentiality restrictions, and registration (www.profilesregistry.nl).

All individuals diagnosed with Hodgkin lymphoma, non-Hodgkin lymphoma or multiple myeloma between 1999-2008 or with endometrial cancer or colorectal cancer between 1998-2007 as registered in the ECR were eligible for participation. However due to the large number of colorectal cancer patients (n=5399) a weighted random selection of 2219 patients based on tumour, sex, and year of diagnosis was made ^{25, 26}. We excluded those patients who had cognitive impairment (based on medical records and advice attending specialist), had unverifiable addresses or had died prior to start of study (according to the ECR, hospital records, and the Central Bureau for Genealogy which collects information on all deceased Dutch citizens via the civil municipal registries). All the studies were approved by the certified Medical Ethics Committee of the Maxima Medical Centre in the Netherlands.

Data collection

Details of the PROFILES data collection method have been described previously ²². In summary, patients were informed about the study via a letter from their (ex)-attending specialist. The letter explained that by completing the questionnaire (online or by pencil-and-paper), patients consented to participate and agreed to the linkage of the questionnaire data with their disease history in the ECR. Non-respondents were sent a reminder letter and questionnaire within two months.

Sociodemographic and clinical characteristics

Patients' sociodemographic and clinical information were available from the ECR. The ECR routinely collects data on tumour characteristics, including date of diagnosis, tumour grade according to the Tumour-Node-Metastasis clinical classification ²⁸, clinical stage ²⁸, treatment, and patient background characteristics including date of birth and comorbidity at the time of diagnosis. Questions on marital status, educational level, and current occupation were added to the questionnaire.

Information provision

To evaluate the information received by cancer patients, the 25-item EORTC QLQ-INFO25 questionnaire was used ²⁹. This questionnaire incorporates four information provision scales and eight single items. The scales are as follows: 1) perceived receipt of information about the disease (four items regarding diagnosis, spread of disease, cause(s) of disease and whether the disease is under control), 2) medical tests (three items regarding purpose, procedures and results of tests), 3) treatment (six items regarding medical treatment, benefits, side-effects, effects on disease symptoms, social life and sexual activity) and 4) other care services (four items regarding additional help, rehabilitation options, managing illness at home, psychological support). The question format was as follows: "During your current disease or treatment, how much information have you received on". The single questions concerned the perceived receipt of written information or information on CDs or tape/video, wanting to receive more or less information, and the satisfaction with the, amount of, and helpfulness of information. The answer categories of the items were "not at all", "a little", "quite a bit", and "very much", except for four items which had a dichotomous (yes/no) scale. After linear transformation, all scales and items range in scores from 0 to 100, with higher scores indicating better perceived information provision ². The questionnaire has been internationally validated, and internal consistency for all scales is good ($\alpha > 0.70$), as is test-retest reliability (intraclass correlations > 0.70) ²⁹. Apart from the EORTC-QLQ-INFO25 questionnaire, two single questions about the use of Internet for seeking additional information were added (i.e., "Do you make use of the Internet?" and "Have you used the

Internet to look for information about cancer?’’), which could be answered with either yes or no.

Type D Personality

Type D personality was measured with the 14-item Type D Personality Scale (DS14)¹⁸. The DS14 is self-administered and takes only a few minutes to complete. The 14 items of this scale are answered on a 5-point response scale ranging from 0 (false) to 4 (true). Seven of these items refer to “Negative Affectivity” (NA) or the tendency to experience negative emotions in general. The remaining 7 items refer to the patient’s level of “Social Inhibition” (SI) or the tendency to inhibit the expression of emotions in social relationships. Patients were categorized as having a Type D personality using a standardized previously established cut-off score of ³10 on both the NA and SI subscales¹⁸, item response theory analyses showed that the DS14 has the highest information around this point³⁰. The DS14 is a valid and reliable scale with Cronbach’s α of 0.87/0.88 in our study sample and a test-retest reliability over a 3-month period of $r = 0.72/0.82$ for the two subscales, respectively¹⁸.

Statistical analyses

Routinely collected data from the ECR on patient and tumour characteristics enabled us to compare the group of respondents, non-respondents and patients with unverifiable addresses, using analysis of variance (ANOVA) for continuous variables and chi-square analyses for categorical variables. Furthermore, differences in sociodemographic, clinical characteristics and *single* items of the EORTC QLQ-INFO25 between patients with and without a Type D personality were also analyzed using ANOVA for continuous variables and chi-square analyses for categorical variables.

The mean subscale scores of the EORTC QLQ-INFO25, stratified by 1) Type D personality, 2) non-Type D personality, were compared by analysis of covariance (ANCOVA). Confounding background variables included for adjustment in these analyses were determined *a priori*³¹ and chosen to be age, sex, years since diagnosis, comorbidity, primary treatment (radiotherapy/chemotherapy) and educational level since previous studies have shown that these factors are related to information provision^{23, 24, 32, 33}. Also, the EORTC QLQ-INFO25 subscale mean scores, stratified by 1) Type D personality (NA+/SI+), 2) SI only (NA-/SI+), 3) NA only (NA+/SI-) 4) the reference group (NA-/SI-), were compared with ANCOVA adjusted for the same variables as described above.

Four multiple linear regression analyses were carried out to investigate the independent association of Type D personality with the EORTC QLQ-INFO25 subscales and one logistic regression analysis was performed to investigate the independent association of Type D personality with satisfaction with the amount of received information (dichotomized item). For the logistic regression analysis, patients were categorized into two groups: (a) patients

who were unsatisfied or only a little satisfied, classified as unsatisfied; and (b) patients who were quite satisfied or very satisfied, classified as satisfied. All regression analyses were adjusted for clinical (years since diagnosis, tumour type treatment, comorbidities) and demographic (age, sex, educational level and marital status) variables and internet use for additional information since previous studies have shown that these factors are related to information provision ^{23, 24, 32, 33}.

All statistical tests were two-sided and considered significant if $p < 0.05$. All analyses were conducted using SPSS version 17.0 (Statistical Package for Social Sciences, Chicago, IL, USA).

RESULTS

Respondents and non-respondents

Three thousand and eighty (69.3%) patients returned a completed questionnaire. A comparison of respondents, non-respondents and patients with unverifiable addresses indicated that patients with unverifiable addresses were younger, with more years since diagnosis, and they were less often treated with surgery, and less often diagnosed with colorectal cancer. Non-respondents were more often female, and were less often treated with radiotherapy or chemotherapy ¹⁹.

Type D, sociodemographic and clinical characteristics

Nineteen percent ($n=572$) of the respondents could be classified as having a Type D personality, 13% ($n=406$) scored above the cut-off for NA only (NA+/SI-) and 17% ($n=512$) for SI only (NA-/SI+). Sociodemographic and clinical characteristics of cancer patients, stratified by patients with 1) Type D personality (NA+/SI+), 2) SI only (NA-/SI+), 3) NA only (NA+/SI-) 4) the reference group (NA-/SI-) are presented in Table 1. Patients with high NA only were more often female compared to the other three groups. Type D cancer patients and patients with high NA only more often reported comorbid diseases compared to cancer patients with high SI only and the reference group. No significant differences between the groups were found in age, years since diagnosis, stage of disease, marital status, educational level, current occupation.

Perceived information provision

The *single* questions of the EORTC QLQ-INFO25 showed that most patients (69%) indicated that they received quite a bit or very much information about the diagnosis (Table 2). Around a third (31%) of the cancer patients stated that they were not or a little informed about the medical treatment of their cancer, almost half (47%) of the patients were not or a little informed about the expected results of treatment and 55% of the patients indicated that they did not receive any information on the possible side effects of their treatment.

Table 1: Sociodemographic and clinical characteristics of cancer patients

	N (%)				
	Reference group (NA-/SI-) N = 1590	Negative affectivity only (NA+/SI-) N = 406	Social inhibition only (NA-/SI+) N = 512	Type D personality (NA+/SI+) N = 572	Overall p-value
Tumour type					0.03
Colorectal cancer	595 (42)	185 (46)	226 (44)	262 (46)	
Endometrial cancer	308 (22)	118 (29)	119 (23)	141 (25)	
Hodgkin lymphoma	80 (6)	18 (4)	23 (5)	25 (4)	
Non-Hodgkin lymphoma	365 (26)	74 (18)	124 (24)	122 (21)	
Multiple Myeloma	60 (4)	11 (3)	20 (4)	22 (4)	
Age at time of survey (mean ± SD)	65.7 (11.8)	66.1 (11.2)	66.3 (11.1)	65.3 (11.4)	0.49
Age at time of survey					0.34
<50 years	129 (9)	28 (7)	45 (9)	47 (8)	
50-70 years	718 (51)	210 (52)	258 (50)	320 (56)	
>70 years	559 (40)	168 (41)	209 (41)	205 (36)	
Years since diagnosis (mean ± SD)	4.6 (2.5)	4.6 (2.6)	4.6 (2.5)	4.4 (2.5)	0.55
Years since diagnosis					0.73
1-5 years	908 (65)	258 (64)	331 (65)	382 (67)	
>5 years	498 (35)	148 (37)	181 (35)	190 (33)	
Sex					<0.001
Male	651 (46)	133 (33)	251 (49)	238 (42)	
Female	757 (54)	273 (67)	261 (51)	334 (58)	
Stage at diagnosis					0.08
I	447 (50)	163 (54)	178 (52)	202 (50)	
II	238 (26)	71 (23)	108 (31)	117 (29)	
III	191 (21)	54 (18)	50 (15)	69 (17)	
IV	27 (3)	15 (5)	9 (3)	15 (4)	
Primary treatment					
Surgery	898 (64)	303 (75)	344 (67)	399 (70)	<0.001
Chemotherapy	528 (38)	135 (33)	164 (32)	182 (32)	0.03
Radiotherapy	373 (27)	110 (27)	144 (28)	145 (25)	0.75
Comorbidity*					<0.001
None	474 (34)	86 (21)	154 (30)	136 (24)	
One	412 (29)	109 (27)	153 (30)	146 (26)	
Two or more	522 (37)	211 (52)	205 (40)	290 (51)	
Marital status					0.89
Partner	1047 (75)	310 (77)	387 (77)	427 (76)	
No partner	341 (25)	92 (23)	118 (23)	137 (24)	
Education level					0.72
University	305 (22)	85 (21)	121 (19)	128 (20)	
Intermediate	413 (30)	130 (33)	161 (32)	170 (31)	
Secondary	429 (31)	131 (33)	147 (29)	169 (31)	
Primary or none	234 (17)	54 (14)	72 (14)	85 (15)	
Current occupation					0.35
Employed	285 (21)	69 (18)	99 (20)	102 (19)	
Unemployed	1066 (79)	326 (83)	396 (80)	448 (82)	

+ adapted Self-administered Comorbidity Questionnaire⁴⁹

Other treatment related information was scarce. Only a few cancer patients (8-18%) indicated that they received quite a bit or very much information about other services (e.g. psychological support, additional help outside the hospital) or things to do to improve their health (23%).

Overall, 41% of the patients were unsatisfied or just a little satisfied with the information they received and 35% found the information a little or not useful at all. Almost a quarter of the patients wanted to receive more information regarding the cause of their cancer, complications and long-term effects of treatment, after care and coping with the disease, and overall information on cancer. More than two-thirds of the patients (71%) stated that they received written information. The internet was used by 1512 participants (52%) of which 1090 participants (72%) had used it to search for additional information about their cancer.

Type D and perceived information provision

Type D cancer patients indicated that they received less information on all *single* items of the EORTC QLQ-INFO25 compared to non-Type D cancer patients ($p < 0.01$), except for expected results of treatment on social and sexual life, psychological assistance and other care locations. There were no significant differences between Type D patients and non-Type D patients in the receipt of written information (69% vs. 71%), wanting less information (5% vs. 3%) and use of internet for additional information (39% vs. 36%). A greater percentage of Type D cancer patients wanted more information compared to non-Type D patients (30% vs. 22%; $p < 0.01$).

The ANCOVA revealed a significant effect of Type D personality on the subscales disease specific information, medical test information, treatment information, satisfaction with received information, and usefulness of information, after adjustment for differences in age, sex, years after diagnosis, comorbidity, primary treatment (radiotherapy/chemotherapy) and educational level (all $p < 0.01$). There was no significant difference between Type D and non-Type D cancer patients on the subscale information about other services.

Additionally, we compared mean EORTC QLQ-INFO25 subscale scores, stratified by patients with 1) Type D personality (NA+/SI+), 2) SI only (NA-/SI+), 3) NA only (NA+/SI-) 4) the reference group (NA-/SI-) (Table 3). Results showed that Type D cancer patients perceived to receive less information about medical tests and score lower on satisfaction with the amount of received information and usefulness of the information compared to the three other groups (all $p < 0.01$). The perceived receipt of disease and treatment information was lower for Type D cancer patients compared to the reference group and patients with NA only (all $p < 0.01$). Patients with SI only perceived to receive less disease information compared to patients with NA only ($p < 0.05$).

Table 2: Perceived information provision characteristics

	N (%)			
	No information at all	A little information	Quite a bit information	Very much information
Disease				
Diagnosis	113 (4)	786 (27)	1422 (49)	578 (20)
Spread disease	306 (11)	877 (31)	1190 (42)	450 (16)
Cause disease	1574 (55)	784 (28)	343 (12)	142 (5)
Under control	168 (6)	761 (27)	1286 (45)	641 (22)
Medical tests				
Purpose test	214 (8)	754 (26)	1334 (47)	544 (19)
Course test	150 (5)	749 (26)	1406 (49)	549 (19)
Results test	87 (3)	614 (22)	1512 (53)	624 (22)
Treatment				
Medical treatment	295 (10)	580 (21)	1289 (46)	665 (23)
Expected result	575 (21)	730 (26)	1099 (40)	346 (13)
Side effects	798 (28)	768 (27)	929 (33)	314 (11)
Expected results on disease symptoms	714 (26)	814 (29)	946 (34)	302 (11)
Expected results on social life	1274 (45)	959 (34)	437 (16)	150 (5)
Expected results on sexual life	1634 (58)	708 (25)	319 (11)	143 (5)
Other services				
Additional help	1609 (57)	763 (27)	326 (12)	126 (5)
Rehabilitation	1866 (67)	565 (20)	269 (10)	90 (3)
Cope with cancer at home	1423 (50)	892 (32)	407 (14)	101 (4)
Psychological assistance	2032 (73)	521 (19)	177 (6)	66 (2)
Single items				
Different care locations	1557 (56)	764 (27)	370 (13)	111 (4)
Things to do to get better	1138 (40)	1036 (37)	513 (18)	128 (5)
	Not satisfied	A little satisfied	Quite a bit satisfied	Very Satisfied
Satisfaction with information	156 (6)	1002 (35)	1251 (44)	444 (16)
	Not helpful	A little helpful	Quite a bit helpful	Very helpful
Helpfulness of information	100 (4)	849 (31)	1318 (48)	506 (18)
	Yes	No		
Received written information	2064 (71)	849 (29)		
Received information on video or cd-rom	147 (5)	2760 (95)		
Wanted more information	659 (23)	2228 (77)		
Wanted less information	98 (4)	2700 (97)		

Multivariate linear regression analyses showed that Type D personality was independently and negatively associated with perceived receipt of information about the disease, information about medical tests and information about treatment, but not with perceived receipt of information about other services. Logistic regression analysis showed that Type D personality was negatively associated with satisfaction with information (Table 4).

Younger age, less years since diagnosis and undergoing chemotherapy were also associated with more perceived information about the disease, medical tests and treatment. Higher educational level and internet use for additional information were associated with more information about the disease and medical tests, while having one or more comorbid diseases was associated with less information about the disease and treatment. Undergoing radiotherapy was associated with more information about the treatment. Finally, less years since diagnosis, chemotherapy, no comorbidities and higher educational level were associated with more satisfaction with the received information (Table 4).

DISCUSSION

To our knowledge, this is the first study that reported on the relationship between Type D personality and information provision among cancer patients. The perceived receipt of information, and the satisfaction with and usefulness of the received information were low in general and even lower for cancer patients with a Type D personality. The perceived receipt of information was lower for Type D cancer patients compared to patients with high scores on NA or SI only and patient with low scores on both NA and SI, also after controlling for demographical and clinical variables. The results were in agreement with our hypotheses.

Table 3: Mean EORTC QLQ-INFO25 subscale scores for those with a Type D personality, those with a high score (≥ 10) on SI only, those with a high score (≥ 10) on NA only, and those with a low score (< 10) on NA and SI.

	Reference group (NA-/SI-) <i>N</i> = 1590	Negative affectivity only (NA+/SI-) <i>N</i> = 406	Social inhibition only (NA-/SI+) <i>N</i> = 512	Type D personality (NA+/SI+) <i>N</i> = 572	Overall <i>p</i> -value
Medical test information	65.0 ^(a)	62.2 ^(b)	60.1 ^(c)	56.3 ^{(a)(b)(c)}	<0.01
Satisfaction with information	61.3 ^(a)	52.9 ^(b)	56.5 ^(c)	49.1 ^{(a)(b)(c)}	<0.01
Helpfulness information	63.9 ^(a)	58.7 ^(b)	58.9 ^(c)	55.0 ^{(a)(b)(c)}	<0.01
Disease information	52.4 ^(a)	51.3 ^(b)	47.5	46.2 ^{(a)(b)}	<0.01
Treatment information	43.3 ^(a)	41.4 ^(b)	38.8	36.6 ^{(a)(b)}	<0.01
Other services	18.7	20.3	17.4	17.6	0.17

^a = Type D patients significantly different from reference group (at least $p < 0.05$);

^b = Type D patients significantly different from patients with NA only (at least $p < 0.05$);

^c = Type D patients significantly different from patients with SI only (at least $p < 0.05$)

Table 4: Multivariate regression analyses evaluating the association of Type D personality with perceived information provision

	Disease information <i>N</i> = 2578 (Beta)	Medical test information <i>N</i> = 2609 (Beta)	Treatment information <i>N</i> = 2470 (Beta)	Other services information <i>N</i> = 2539 (Beta)	Satisfaction with information <i>N</i> = 2682 (Odds ratio)	Helpfulness of information <i>N</i> = 2533 (Odds ratio)
Type D personality						
Non-Type D	Reference	Reference	Reference	Reference	Reference	Reference
Type D	-0.09**	-0.12**	-0.08**	-0.02	0.54 (0.44-0.66)**	0.58 (0.47-0.72)**
Age	-0.10**	-0.07*	-0.14**	-0.12**	0.99 (0.98-1.00)	0.99 (0.97-0.99)**
Years since diagnosis	-0.07**	-0.08**	-0.07**	-0.12**	0.93 (0.90-0.96)**	0.94 (0.91-0.98)**
Tumour type						
Colorectal cancer	Reference	Reference	Reference	Reference	Reference	Reference
Endometrial cancer	0.09**	0.01	0.10**	-0.04	1.49 (1.18-1.88)**	1.03 (0.80-1.32)
Hodgkin lymphoma	0.02	0.01	0.01	-0.02	1.49 (0.93-2.37)	2.14 (1.18 -3.90)*
Non-Hodgkin lymphoma	0.03	0.01	0.02	-0.04	1.37 (1.09-1.71)**	1.25 (0.98-1.60)
Multiple Myeloma	0.01	0.01	0.01	-0.01	1.21 (0.78-1.86)	0.78 (0.49 – 1.23)
Sex						
Male	Reference	Reference	Reference	Reference	Reference	Reference
Female	0.02	0.03	-0.01	0.01	0.88 (0.73-1.07)	1.07 (0.87-1.32)
Radiotherapy						
Yes	Reference	Reference	Reference	Reference	Reference	Reference
No	-0.02	-0.04	-0.11**	-0.04	0.96 (0.80-1.15)	0.87 (0.71-1.06)
Chemotherapy						
Yes	Reference	Reference	Reference	Reference	Reference	Reference
No	-0.07**	-0.06*	-0.26**	-0.17**	0.71 (0.58-0.88)**	0.74 (0.59-0.93)*
Co morbidity						
None	Reference	Reference	Reference	Reference	Reference	Reference
One	-0.06*	-0.04	-0.05*	0.02	0.94 (0.75-1.19)	0.92 (0.71-1.18)
Two or more	-0.07**	-0.04	-0.06*	0.05*	0.68 (0.55-0.84)**	0.76 (0.61-0.96)*
Educational level						
University	Reference	Reference	Reference	Reference	Reference	Reference
Intermediate	-0.03	-0.07*	-0.05	-0.01	0.89 (0.69-1.14)	0.92 (0.70-1.20)
Secondary	-0.08**	-0.11**	-0.07*	-0.01	0.71 (0.55-0.91)**	0.63 (0.49-0.83)**
Primary or none	-0.07*	-0.09**	-0.04	0.05	0.78 (0.60-1.02)	0.84 (0.63-1.12)
Marital status						
Partner	Reference	Reference	Reference	Reference	Reference	Reference
No partner	0.04*	0.03	0.04**	-0.04*	0.95 (0.78-1.15)	0.85 (0.69-1.04)
Employment						
Unemployed	Reference	Reference	Reference	Reference	Reference	Reference
Employed	-0.02	0.01	0.01	-0.03	0.95 (0.74-1.23)	1.06 (0.81-1.40)
Internet use for information						
Internet	Reference	Reference	Reference	Reference	Reference	Reference
No internet	-0.09**	-0.08**	-0.06	-0.02	0.91 (0.75-1.09)	0.70 (0.58-0.86)**

* $p < 0.05$; ** $p < 0.01$

Type D cancer patients perceived to receive less information compared to non-Type D's. Individuals with a Type D personality tend to use more maladaptive, passive coping strategies such as resignation, denial, avoidance or withdrawal³⁴⁻³⁶ and will not seek for support and information actively³⁶. Even if the doctor gives a large amount of information, it might be possible that the passive coping style leads to inadequate information processing, whereby the relevant information will not be picked up. Previous research showed that people experiencing higher levels of negative affect had difficulty with their attempts to access, obtain, and understand cancer information³⁷. Individuals with high scores on neuroticism, who might also have high scores on NA¹⁸, have a preference for information that reassures them³⁸ and will probably not seek out other information. Cancer related information might be judged as threatening by patients with high scores on NA and this will probably be accompanied by the experience of more negative emotions. The experience of negative emotions requires energy and can distract attention and diminish concentration. The recall of the received information could therefore be hindered. The perceived receipt of less information by Type D cancer patients could have resulted in lower levels of satisfaction with the received information and their indication that they wanted to receive more information as compared to non-Type D cancer patients.

Furthermore, patients with a Type D personality tend to be more socially withdrawn than non-Type D's, resulting in less social support³⁹. Social support of a companion during the doctor-patient conversation has been found to increase patient understanding and involvement in consultation⁴⁰, and will possibly also affect the recall of information. Previous studies also showed that one aspect of SI is feeling insecure and less competent when communicating with others^{35, 41}. These feelings might result in a lower willingness to ask questions during a consultation. Type D patients may not follow through to get the information from their health care provider when their information needs are not met. Another interesting observation in this context is that the perceived receipt of written information and the use of internet to search for additional information did not differ between Type D and non-Type D cancer patients in our study. This supports the idea that Type D cancer patients are less competent in actively communicating with their health care provider. In addition, the information needs of cancer patients with a Type D personality might differ from the needs of non-Type Ds, since a recent study showed that Type D cancer patients experienced worse illness perceptions and found their illness less comprehensible compared to non-Type Ds²⁰.

Future research should try to identify the specific information needs of cancer patients with a Type D personality. The Type D scale can probably be used as a screening tool in cancer patients to identify subgroups at risk for inadequate information provision. Type D cancer patients may benefit from behavioural interventions that are aimed towards reducing maladaptive coping strategies such as withdrawal¹⁵. Such an intervention should focus on

the empowerment of Type D patients to increase their health control and to reduce negative emotions ³⁶. Giving special attention to patients with a Type D personality is important because both inadequate information provision and Type D personality are independently associated with worse health outcomes ^{1, 17, 42-44}. It would also be interesting to investigate in future research whether health care practitioners identify Type D patients as a difficult group to work with.

This study has some limitations that should be noted. Although information was present concerning the demographic and clinical characteristics of the non-respondents and patients with unverifiable addresses, whether non-respondents more often had a Type D personality remains unknown. In addition, although Type D personality is a stable construct ⁴⁵, the cross-sectional study design limits the determination of causal associations between the study variables. Furthermore, the validity of the cut-off scores used for the dichotomization of Type D personality has not been tested in cancer patients. Recent taxometric analyses have suggested that Type D may be better represented as a dimensional construct ⁴⁶. This does not necessarily imply that dichotomization is inappropriate. The Type D construct has never inferred a true taxon that is defined by discontinuity between groups on an underlying dimension, and individuals belong only probabilistically to Type D and non Type D categories ¹⁶. Rather, Type D refers to similar patterns of standing along the NA and SI dimensions that do occur across patients, and dichotomization helps to identify Type D patients who are more similar to their subgroup's personality profile than non-Type D patients. Dimensional and categorical approaches to Type D do not need be to mutually exclusive, but rather represent two different ways of capturing psychological tendencies of individuals that warrant more research ⁴⁷.

Also, this study relies on self-report measures of information provision and it is not clear how much information was actually provided. The passive coping style of Type D cancer patients, including denial and avoidance, could lead to underreporting of the received information. It would therefore also be interesting to compare data on actual information provision with self-report data from questionnaires. Furthermore, the mean time since diagnosis was 4.6 years, which could hinder the recall of information received. Patients often forget a substantial amount of the information given because the information is complex and emotionally charged ⁴⁸. Since the patients in the current study can be described as patients who are out of the acute phase of medical treatment and decision making, the results cannot be generalized to patients who are in the midst of their treatment phase or shortly after treatment completion. For future research, it would be interesting to compare the responses of patients in the midst of their treatment to determine possible differences between Type D and non-Type D's in recall bias.

A frequently reported unmet need is information about after care³. In our study the perceived receipt of information about other services was low for all patients and we therefore could not identify differences between Type D and non-Type D patients on this scale.

One of the strengths of our study is the high response rate among the different population-based tumour groups that facilitates generalizing the results to a larger population of cancer patients. In addition, we evaluated a broad spectrum of possible confounding factors, including age at time survey, years since diagnosis, sex, marital status, educational level, primary treatment and comorbidity.

In conclusion, this study showed that patients with a Type D personality perceived to receive less information and reported less satisfaction with the amount of received information as compared to non-Type D patients. Future research could focus on the effectiveness of tailored communication possibly in combination with a behavioral intervention to teach Type D patients how to deal with cancer related information.

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CHAPTER 4

The relation between information provision and health-related quality of life, anxiety and depression among cancer survivors: a systematic review

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ABSTRACT

Background: Providing information, that is congruent with patients' needs is an important determinant for patient satisfaction and might also affect health related quality of life (HRQoL), anxiety and depression levels of cancer survivors.

Design: The authors systematically reviewed the available literature on the relationship between information provision and health-related quality of life, anxiety and depression. A PubMed literature search for original articles published until February 2010 was performed. Twenty-six articles, all conducted between 1996 and 2009, which met the predefined inclusion criteria, were subjected to a quality checklist.

Results: Satisfied patients, patients with fulfilled information needs, and patients who experience less information barriers, in general have a better HRQoL and less anxiety and depression. Out of eight intervention studies that aimed to improve information provision, only one showed a positive association with better HRQoL.

Conclusion: Health care providers must pay more attention to patient-centered information provision. Additional research is needed to make definitive conclusions about information interventions, as most results did not reach statistical significance due to methodological constraints. The quick development of the relatively young research field of patient reported outcomes in cancer survivorship will make it possible to conduct better quality studies in the future.

INTRODUCTION

The provision of information to patients is one of the most important factors of supportive cancer care, across the whole cancer continuum. The goal of providing information is to prepare patients for their treatment, to increase adherence to therapy and to increase their abilities to cope with the illness and to promote recovery ¹. However, the results of a systematic review show that 6 to 93 percent of the cancer patients report adequate information provision as an unmet need throughout their cancer experience ². Patients frequently report barriers to receive the information needed ³. Health care providers are often still reluctant to give the full amount of information about cancer and its treatment, while the majority of cancer patients want as much information as possible about their disease, treatment and rehabilitation ³. The information needs of cancer patients vary by gender, age, cultural background, educational level, cancer type, stage of disease and coping style ^{4,5}. Providing information, that is congruent with patients' needs is an important determinant for patient satisfaction and might also affect health related quality of life (HRQoL) and anxiety and depression levels of cancer patients.

HRQoL is a multidimensional construct that covers the patients' perceptions of his or her physical, emotional, social, and cognitive functions. HRQoL assessment is an important aspect of cancer care. HRQoL parameters providing prognostic information can facilitate clinical decision making in terms of better treatment selection for cancer patients ⁶⁻⁸. Furthermore, cancer survivors often deal with adaptation problems and assessment of their HRQoL could help to improve aftercare ⁹. Cancer survivors experience high levels of psychological distress; a range of feelings and emotions that people experience in reaction to cancer including depression and anxiety, with an important impact on HRQoL ^{10, 11}. In the last decade, the role of information provision in cancer care has been acknowledged. Several studies have investigated the relationship between information provision and HRQoL, anxiety and depression, but results seem inconsistent ¹². The evaluation of a possible relationship between HRQoL and information provision is difficult because of the conceptualization of both constructs and methodological challenges in measuring these constructs. Throughout this review, information provision is defined as all cancer related information provided by the health care provider/nurse in oral, written or other form. From the perspective of the patient, information provision is mostly measured in terms of 'satisfaction with received information', 'barriers to receive information', 'information needs' and 'information quality' and 'information clarity'. Importantly, this review did not focus on information disclosure regarding the initial cancer diagnosis or end of life issues. The goal of our review is to provide a complete overview of the literature on the impact of information on the HRQoL, anxiety and depression levels of cancer survivors. We used the definition of

the US National Coalition for Cancer Survivorship that defines a person as a survivor from the moment of diagnosis through the balance of his or her life (<http://www.canceradvocacy.org/about/org/>). We hypothesize that better information provision (fulfilled needs, less barriers, clear and high quality information) is related to higher satisfaction levels of cancer survivors regarding information which may impact HRQoL, especially mental health, anxiety and depression levels.

METHODS

Search strategy

A computerized search of the literature through the search engines Pubmed and PsychINFO was performed on December 3, 2009. The search strategy combined the term 'cancer' with other key terms related to information provision and HRQoL. For 'information provision' we included the terms information, information provision, information disclosure, information needs, information satisfaction, information level, information barriers, written information, oral information, audiotape information, CDROM. For the constructs of HRQoL, anxiety and depression we included the terms quality of life, health related quality of life, health status, well-being, anxiety and depression.

The reference lists of all identified publications were checked to retrieve other relevant publications, which were not identified by means of the computerized search. There were no restrictions with regard to the years of publication. The search yielded 5732 hits.

Selection criteria

Studies that met the following criteria were included: (1) if they evaluated the relation between information provision and HRQoL, anxiety and depression in adult cancer survivors, and this evaluation was one of the key objectives of the study (2) if the publication was an original article (e.g. no poster abstract, letter to the editor etc.), (3) if the article was a full report published in English and (4) if it was published in a peer-reviewed journal. Studies were excluded for the following reasons: (1) if they were individual case reports or articles that reviewed the literature, (2) if the study was focused on end-stage cancer patients (terminal ill patients), because this patient group is dealing with specific end-of-life issues, (3) if the study focused on communication aspects (e.g. body language), (4) if the study focused on information provision to family members, (5) if the study focused on diagnosis or prognosis as primary information measure, or if (6) HRQoL was measured with one single item and was not a part of a validated questionnaire.

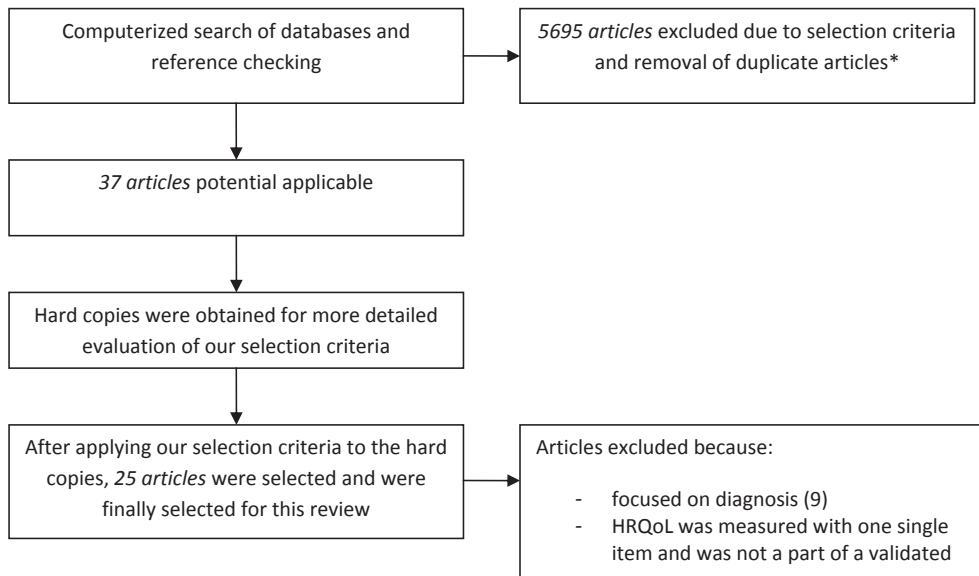


Figure 1: Flow diagram of papers accepted and rejected during selection procedure.

* The selection criteria are described in the methods section.

The described inclusion and exclusion criteria were applied to our initial 5732 hits. Based on their titles and abstracts, 37 articles met our criteria. The 37 hard copies were obtained and reviewed by three investigators. After careful review, 25 articles fulfilled our selection criteria and were included in this review¹²⁻³⁶. The flow-chart of this selection procedure is shown in Figure 1.

Quality assessment

The methodological quality of each of the selected articles was independently assessed, by all three investigators based on established criteria for systematic reviews (Table 1)^{37,38}. Each item of a selected study, that matched our criteria, was assigned one point. If an item did not meet our criteria or was described insufficiently or not at all, zero points were assigned. The highest possible score was 13. Studies scoring 10 points or more were arbitrarily considered to be of 'high quality'. Studies scoring between 6 and 10 points were rated as 'adequate quality'. Studies scoring less than 6 points were considered to be of 'low quality'.

Table 1: List of criteria for assessing the methodological quality of studies on HRQoL, anxiety, depression and information provision among cancer survivors

Positive if with respect to
HRQoL
1. A valid (health-related) quality of life, health status, anxiety or depression questionnaire is used. If items were deleted from the valid questionnaire, the new questionnaire must be validated.
Information assessment
2. A valid “information provision” questionnaire is used. If items were deleted from the valid questionnaire, the new questionnaire must be validated.
Study population
3. A description is included of at least two socio-demographic variables (e.g., age, employment status, educational status).
4. A description is included of at least two clinical variables of the described patient population (e.g., tumour stage at diagnosis, treatment).
5. Inclusion and/or exclusion criteria are described.
6. Participation and response rates for patient groups have to be described and have to be more than 75%.
7. Information is given about the degree of selection of the patient sample (information is given about the ratio respondents versus non-respondents).
Study design
8. The study size is consisting of at least 50 patients (arbitrarily chosen).
9. The data is prospectively gathered.
10. The process of data collection is described (e.g., interview or self-report etc.).
Results
11. The results are compared between two groups or more (e.g., healthy population, groups with different treatment or age) and/or results are compared between at least two time points (e.g., pre- versus post-treatment).
12. Mean, median, standard deviations or percentages are reported for the most important outcome measures.
13. Statistical proof for the findings is reported.

RESULTS

Study characteristics

In total, 25 studies were included, all published between April 1996 and December 2009. Different questionnaires with different outcome measures to assess HRQoL, anxiety and depression were used. All studies used different instruments to measure one or more aspects of information provision. Prospective, cross-sectional, observational as well as intervention studies were included. The main findings are summarized in Table 2.

Methodological quality

The evaluation of the methodological quality of the studies by the three reviewers yielded disagreement on some items, mostly due to differences in interpretation. These were solved through discussion in a consensus meeting. The quality scores ranged from 7 to 13 points (Table 2) and the mean quality score was 9.6. None of the studies had a low quality. Thirteen studies had a high quality^{15, 17, 21, 22, 24, 26-28, 30, 31, 35, 36}. The remaining twelve studies had an adequate quality^{12-14, 16, 18-20, 25, 29, 32-34}. General shortcomings of the included articles were the absence of a validated “information” questionnaire, absence of information about the degree of selection of the patient sample, a cross-sectional design, and the lack of comparison between two groups or time points.

Health-related quality of life

Fifteen studies, 5 prospective and 10 cross-sectional, examined the relation between information provision and HRQoL^{12-14, 16-20, 26-29, 34-36}. Three prospective studies found a positive association between information satisfaction and HRQoL^{12, 27, 35}. A Swedish study of 36 patients with a carcinoid tumour, showed a positive relation between satisfaction with doctors’ provision of information and emotional function and global quality of life (QoL) at three of the four time points¹². In a study among 82 head and neck cancer patients, satisfaction with information before treatment was predictive of better Mental Component Summary scores 6-8 months after the end of treatment, but not to the Physical Component Summary scores²⁷. The third study among 211 Chinese nasopharyngeal carcinoma patients found that more satisfaction with the medical information provided one month after the end of radiotherapy, was related to a better QoL four months later³⁵.

Two other prospective studies focused on the clarity and quality of the information provided, and the need for information. Breast cancer patients reporting unclear information provision scored significantly worse, up to 4 years after diagnosis, on 17 of the 27 QoL variables, including emotional functioning, social functioning and global QoL²⁶. Breast cancer patients who rated their level of information at baseline as high, experienced higher quality of life after three ($p < .001$) and six months ($p = .049$)³⁶. Overall, prospective studies showed that satisfied patients, patients who reported to receive clear and high levels of information, reported better mental HRQoL and global HRQoL. Positive associations between information provision and physical HRQoL have not been found.

Five out of six cross-sectional studies found a positive relation between information satisfaction and HRQoL^{13, 17-20, 28}. Two studies among breast cancer survivors found a strong positive association between satisfaction with treatment and survivorship information and mental health and vitality^{20, 28}. A British study among 102 breast cancer and 112 prostate cancer patients concluded that after controlling for demographic and disease characteristics,

information satisfaction explained 21% of the variance in global QoL, 12% in physical well-being, 13% in social well-being, 8% in emotional well-being, and 10% in functional well-being (all $p < 0.001$)¹⁸. This study, and an Italian study among a varied sample of 175 cancer patients, also found a positive association between satisfaction with information received and QoL^{13, 18}. Besides, the Italian study found no differences in QoL of adequately versus inadequately informed patients¹³. A French study of cancer patients with different diagnoses showed that higher global scores for QoL were related to higher satisfaction with all aspects of care, including the information provision¹⁷. Contradictory, lower physical and emotional functioning also predicted higher satisfaction with the doctors' information provision in this study. One cross-sectional study among 30 cancer patients undergoing chemotherapy found no differences in QoL between satisfied and dissatisfied patients¹⁹.

Four other cross-sectional studies focused on the clarity and quality of the information provided, and the need for information^{14, 16, 29, 34}. Worse physical and emotional functioning were significantly associated with worse ratings of information quality, more barriers to obtain information and a greater need for information in two large American studies among a sample of diverse cancer survivors^{16, 29}. Breast cancer patients who reported greater difficulty in accessing needed information or had greater unmet information needs experienced lower emotional, functional, and social well-being and worse physical, cognitive and role functioning as well as lower perceptions of health competence ($p < 0.01$)^{14, 34}. In the cross-sectional studies better mental, physical and global HRQoL were associated with fulfilled informational needs, satisfaction with the received information, the receipt of good quality and clear information and less information barriers. However, one study found no difference in HRQoL¹⁹ and one study reported conflicting results¹⁷.

Anxiety and depression

Five studies, three prospective and two cross-sectional, focused on anxiety and depression in relation to information provision^{12, 25, 27, 33, 36}. A study of 82 head- and neck cancer patients found satisfaction with information before treatment, to be predictive of depression but not anxiety, 6-8 months after the end of treatment²⁷. However, a study of 36 carcinoid tumour patients found a negative relation between satisfaction with doctors' provision of information and anxiety and depression at the first three of four time points (T1-T3)¹². Breast cancer patients who rated their level of information at baseline as high were less depressed after three ($p = .010$) and six months ($p < .001$)³⁶. The studies with a prospective design showed that, satisfaction with the received information and less information needs were independently related to less anxiety and depression.

The receipt of information was positively associated with the cancer patients' physical condition and negatively with mood and depression in a Finnish cross-sectional study³³. A

study among breast, prostate, cervical and laryngeal cancer patients showed that patients who were dissatisfied with the received information were much more likely to be depressed and were marginally more likely to be anxious²⁵. The results of the cross-sectional studies support the results of the prospective studies.

Interventions

Some studies examined the effect of different information interventions on the HRQoL or depression and anxiety levels of cancer patients^{15, 21-24, 30-32}. In a Swedish study, 210 consecutive cancer patients were randomized to one of three information conditions before the start of curative radiation treatment²³. Compared to patients receiving standard information or standard information plus an extra brochure, patients who received standard information plus group and repeated individual information were significantly more satisfied with the information. However, there were no differences with respect to anxiety, depression, subjective distress and QoL. A Dutch study investigated the effects of the Interactive Breast Cancer CDROM, compared to the standard oral information, as a decision aid for 180 breast cancer patients with a choice between breast conserving therapy and mastectomy³⁰. An overall positive effect of the CDROM was found on satisfaction with the general and breast cancer-specific information received. Further, an overall positive effect of the CDROM condition was found on generic QoL as well as on breast-specific QoL. Subsequent analyses revealed that at 3 and 9 months follow-up patients in the CDROM condition reported better general health than control patients. Additionally, at 9 months follow-up, the CDROM condition reported better physical functioning, and less pain and arm symptoms.

Three studies tested the efficacy of an audio-taped consultation on the QoL of cancer patients showing no main effect of the intervention on QoL or mood state^{21, 22, 31}. The first study showed that the provision of a taped initial consultation resulted in more satisfied patients than patients allocated to the control group³¹. The other two studies among breast and prostate cancer patients showed that the provision of an audiotape of their primary treatment consultation was not significantly related to patient satisfaction with communication and was not significantly affected by choice of receiving the audiotape²¹. Furthermore, the compliance was low with 40% of the patients who did not listen to the audiotapes, mainly because they felt emotionally not prepared to listen²¹. However, patients rated the audiotape intervention positively. Patients receiving the consultation audiotape reported having been provided with significantly more disease and treatment information in general and more information about treatment alternatives and treatment side effects in particular, than patients who did not receive the audiotape²².

A Greek study of 145 cancer patients who were randomized to receive a booklet about chemotherapy or not, showed that patients provided with the information booklet reported significantly higher rates of satisfaction with information than the control group, felt better and more informed, and perceived the information received as being clearer and more detailed ²⁴. However, no significant benefits in anxiety, depression and QoL occurred. Another study randomized patients to receive oral information only or oral plus written information describing the disease and its associated surgery and outcomes ¹⁵. There was no significant difference in QoL at baseline, during the postoperative period or at 3 months post surgery. In addition, the QoL scores for each dimension (anxiety, depressed mood, positive well-being, self-control, general health, and vitality) were not statistically different between both groups at each time of analysis.

In a cluster randomized trial, no statistically significant effects of a Point of Information and Support (PIS) on anxiety or dissatisfaction levels was observed ³². However, 52% of centers in the experimental group did not implement the PIS in accordance with the protocol. The same study highlighted that a greater likelihood of dissatisfaction was associated with the presence of anxiety and/or depression ³².

DISCUSSION

The aim of this systematic review was to summarize and evaluate the results of all studies focussing on the relationship between information provision and HRQoL and psychological distress. All five prospective observational studies found a positive relation between appropriate information provision (satisfaction with the received information, fulfilled informational needs, high quality and clear information) and mental and global HRQoL and a negative relation between appropriate information provision and depression and anxiety. The results of all 12 cross-sectional observational studies are in accordance with the findings of the prospective studies, however they also found a positive association between appropriate information provision and physical HRQoL. Only one out of eight intervention studies found a positive effect of information on HRQoL.

The prospective observational studies found a strong positive relation between adequate information provision and mental health but not physical health. A better understanding of a patients' situation after the information provision or the receipt of information aimed at learning to cope with cancer or reducing distress might be responsible for better mental health and lower levels of anxiety and depression ³⁵. Patients who had difficulties in obtaining the information they desire were found to have less confidence in their ability to deal with health-related issues ¹⁴.

Table 2: Overview of all included studies sorted on outcome

First author [ref], country, year	Design	Study population	HRQoL, anxiety and/or depression instrument	Information provision instrument	Results	Quality score
Health related quality of life (HRQoL)						
Frodj ¹² , Sweden, 2009	Prospective	36 carcinoid tumour patients	- EORTC QLQ-C30*	Comprehensive Assessment of Satisfaction with Care (CASC)	Satisfaction with doctors' provision of information was positively related to emotional function, global QoL at T1-T3.	9
Llewellyn ²⁷ , UK, 2006	Prospective	82 newly diagnosed head and neck cancer patients; 47% had an early stage (1 or 2)	General Health Survey Questionnaire, Short Form (SF-12)	Satisfaction with information profile (SCIP)	Satisfaction with information before treatment was predictive of mental component summary scores 6-8 months after the end of treatment, but not of physical component scores.	13
Yu ³⁵ , China, 2001	Prospective	211 nasopharyngeal carcinoma patients; 41% had an early stage (I or II), 59% had a higher stage	Functional Assessment of Cancer Therapy-General (FACT-G)	Medical Interview Satisfaction Scale (MISS)	More satisfaction with the medical information provided an average of 1 month after the end of radiotherapy had a better QoL 4 months later.	10
Kerr ²⁶ , Germany, 2003	Prospective	980 breast cancer patients, 93.3% had an early stage (I, I, or II)	- EORTC QLQ-C30* - EORTC BR-23 (breast cancer specific)	Self-developed: Satisfaction with hospital stay, doctor communication and aftercare	17 QoL variables were significantly worse, up to 4 years after diagnosis, for those patients reporting unclear information.	11
Vogel ³⁶ Germany, 2009	Prospective	135 breast cancer patients	- EORTC QLQ-C30*	- Patient satisfaction with communication 25 item Likert scale - Self developed question about level of information	Patients who rated their level of information at baseline as high experienced a higher QoL after 3 and 6 months.	10
Griggs ²⁰ , USA, 2007	Cross-sectional	235 breast cancer patients	- Medical Outcomes Study Short Form 36 (SF-36) - Impact of Events Scale (IES)	Self-developed: Satisfaction with information	Strong positive relationship between satisfaction with information and vitality, mental health, and a strong negative relationship with distress.	9
Mallinger ²⁸ , USA, 2005	Cross-sectional	182 breast cancer survivors	Medical Outcomes Study Short Form 36 (SF-36)	Information needs scale for recently diagnosed breast cancer patients	Better mental health is associated with greater satisfaction with information about treatment and survivorship.	10

Table 2: Overview of all included studies sorted on outcome (*Continued*)

First author [ref], country, year	Design	Study population	HRQoL, anxiety and/or depression instrument	Information provision instrument	Results	Quality score
Davies ¹⁸ , UK, 2008	Cross-sectional	-102 breast cancer -112 prostate cancer patients	Functional Assessment of Cancer Therapy (FACT-G)	Adapted version of the Information Satisfaction Questionnaire (ISQ)	Information satisfaction is a predictor of global QoL and its four dimensions. Satisfaction is positively associated with QoL.	9
Annunziata ¹³ , Italy, 1998	Cross-sectional	175 patients (breast, gastrointestinal, leukemia, genitourinary tumors, lung, other neoplasms)	- Functional Living Index for Cancer (FLIC) - State-Trait Anxiety Inventory (STAI)	Degree of information on diagnosis and status of disease	Level of information did not affect QoL, satisfaction with information was associated with better QoL.	8
Bredart ¹⁷ , France, 2001	Cross-sectional	97 cancer patients with different diagnoses and stages	EORTC QLQ-C30*	Comprehensive Assessment of Satisfaction with Care (CASC)	Lower physical functioning and emotional functioning predicted higher satisfaction with doctor's information provision.	11
Elf ¹⁹ , Sweden, 2001	Cross-sectional	30 cancer patients undergoing chemotherapy	EORTC QLQ-C30*	-Self developed: questions on patients' satisfaction with information - Miller Behavioral Styles Scale (MBSS)	No significant differences in quality of life could be found between satisfied and dissatisfied patients.	9
Beckjord ¹⁶ , USA, 2008	Cross-sectional	1040 cancer survivors (bladder, leukemia, colorectal, NHL)	Medical Outcomes Study Short Form 36 (SF-36)	Self-developed: information needs	More information needs were associated with worse perceived mental and physical health.	8
McInnes ²⁹ , USA, 2008	Cross-sectional	778 cancer survivors of 6 common cancers (bladder, breast, colorectal, prostate, uterine, melanoma); 3.1% in situ, 72.6% localized, 22.8% regional, 1.5% distant	Medical Outcomes Study Short Form 36 (SF-36)	Self-developed scales: information quality, information barriers, information needs	Worse physical and mental functioning was associated with greater need for information, worse ratings of information quality, and more barriers in obtaining information.	9
Arora ¹⁴ , USA, 2002	Cross-sectional	225 breast cancer patients; 80.4% had an early stage (I, I, or II)	Functional Assessment of Cancer Therapy (FACT)	Barriers to information access scale (BIAS)	Experience of greater barriers to accessing needed health information was significantly associated with lower emotional, functional and social/family well-being.	7

Table 2: Overview of all included studies sorted on outcome (*Continued*)

First author [ref], country, year	Design	Study population	HRQoL, anxiety and/or depression instrument	Information provision instrument	Results	Quality score
Snyder ³⁴ , USA, 2007	Cross-sectional	117 cancer patients (breast, lung, prostate), 35.3% had an early stage, 14.7 loco-regional, 50% metastatic	EORTC-QLQ-C30*	Supportive Care Needs Survey (SCNS)	Better emotional (not physical function) was associated with fewer unmet information needs.	7
Anxiety and/or depression						
Llewellyn ²⁷ , UK, 2006	Prospective	82 newly diagnosed head and neck cancer patients, 47% had an early stage (1 or 2)	- Hospital Anxiety and Depression Scale (HADS)	Satisfaction with information profile (SCIP)	Satisfaction with information before treatment was predictive of depression 6-8 months after the end of treatment, but not of anxiety.	13
Frodj ¹² , Sweden, 2009	Prospective	36 carcinoma tumour patients	- Hospital Anxiety and Depression Scale (HADS)	Comprehensive Assessment of Satisfaction with Care (CASC)	Satisfaction with doctors' provision of information was negatively related to anxiety and depression at T1-T3.	9
Vogel ³⁶ , Germany, 2009	Prospective	135 breast cancer patients	- Hospital Anxiety and Depression Scale (HADS)	- Patient satisfaction with communication 25 item Likert scale - Self developed question about level of information	Patients who rated their level of information at baseline as high were less depressed after three and six months.	10
Sainio ³³ , Finland, 2003	Cross-sectional	273 cancer patients (81 breast, 73 haematological, 119 other); 35% the cancer had recurred or metastases had appeared	Depression Scale (DEPS)	Self-developed questionnaire containing questions about obtained information and method of providing information	Both the respondents' physical condition (positive) and depression (negative) were associated with receiving information.	9
Jones ²⁵ , UK, 1999	Cross-sectional	525 cancer patients (309 breast, 129 prostate, 22 cervical, 65 laryngeal)	Hospital Anxiety and Depression Scale (HADS)	One question about satisfaction with information given	Depression was a predictor of dissatisfaction with information.	9

Table 2: Overview of all included studies sorted on outcome (*Continued*)

First author [ref], country, year	Design	Study population	HRQoL, anxiety and/or depression instrument	Intervention studies		Results	Quality score
					Information provision instrument		
Hagglmark ²³ , Sweden, 2001	Prospective	231 cancer patients (breast, bladder, prostate)	- Hospital Anxiety and Depression (HADS) scale - Impact of Event Scale (IES) - Cancer Inventory of Problem Situations (CIPS II)	Self developed: Satisfaction with information questionnaire		No relation satisfaction and anxiety and depression.	10
Molenaar ³⁰ , the Netherlands, 2001	Prospective	180 breast cancer patients	- Medical Outcomes Study 20 (MOS20) - EORTC QLQ-BR23 (breast cancer specific)	Self developed: Two instruments to measure satisfaction with information (general and treatment specific)		CDROM patients were more satisfied with breast cancer- specific information. At 3 and 9 months, a positive effect was found on general health. At 9 months CDROM patients reported better physical func- tioning, less pain and fewer arm symptoms.	11
Ong ³¹ , the Netherlands, 2000	Prospective	201 cancer patients (gynaecologic or internal)	- Medical Outcomes Study 20 (MOS20) - Rotterdam Symptom Checklist	Patient Satisfaction Questionnaire		Patients provided with audio- tape initial consultation were more satisfied than patients without the tape. The inter- vention did not have an effect on QoL.	10
Hack ²¹ , Canada, 2003	Prospective	628 breast cancer patients	- Functional Assessment of Cancer Therapy (FACT-B) - Profile of Mood States (POMS)	Patient Perception Scale		Audiotape of primary adju- vant treatment consultations to women with breast cancer was not significantly related to patient satisfaction with communication, mood state, or QoL at 12 weeks post-con- sultation, and was not signifi- cantly affected by choice of receiving the audiotape.	10

Table 2: Overview of all included studies sorted on outcome (*Continued*)

First author [ref], country, year	Design	Study population	HRQoL, anxiety and/or depression instrument	Information provision instrument	Results	Quality score
Hack ³² , Canada, 2007	Prospective	425 prostate cancer patients; 76.2% had an early stage (I, or II), 14.6% had a high stage (III or IV)	- Functional Assessment of Cancer Therapy (FACT-P) - Profile of Mood States (POMS)	Patient Perception Scale	Audiotape of primary adjuvant treatment consultations to women with breast cancer was not significantly related to patient satisfaction with communication, mood state, or QoL at 12 weeks post-consultation, and was not significantly affected by choice of receiving the audiotape.	11
Iconomou ²⁴ , Greece, 2005	Prospective	145 cancer patients (lung, breast, colorectal, genitourinary, other); 50% had limited disease and 50% had advanced disease	- EORTC-QLQ-C30* - Hospital Anxiety and Depression Scale (HADS)	Single question about satisfaction with information provision	Patients provided with the information booklet reported significantly higher rates of satisfaction with information than control group, felt better and more informed, and perceived information received as being clearer and detailed. No significant benefits in anxiety, depression, QoL.	11
Barlesi ¹⁵ , France, 2008	Prospective	75 non-small cell lung cancer patients	Psychologic Global Well-Being Index (PGWBI)	- Questionnaire of satisfaction of hospitalized patients (QSH) - Self developed: question information satisfaction	No differences in QoL between non-small cell lung cancer patients receiving oral information only as compared with oral plus written information.	10
Passalacqua ³² , Italy, 2009	Prospective	3197 cancer patients	Hospital Anxiety and Depression Scale (HADS)	One single question about satisfaction with received information	The per protocol analysis did show a reduction in psychological distress and dissatisfaction, for the patients in the PIS group compared to the control group, but differences were not significant.	9

*EORTC = European Organization for Research and Treatment of Cancer

Appropriate information provision lead to an improved health competence, a better sense of control over cancer, and better symptom management ^{14, 20}. From the cross-sectional observational studies the direction of the relationship is not clear. A lack of information, or information of low quality, can lead to anxiety, depression or a decreased mental and/or global HRQoL as suggested by the prospective studies. However some information can elevate patients' distress levels ³⁹. On the other hand anxiety can inhibit information processing, patients with a poorer mental health may have more difficulty to understand the information even when the information is of high quality, while patients with better global health are more satisfied beforehand because of their better emotional state ^{20, 40}.

The results of the observational studies were not confirmed by the intervention studies. This can be explained by the nature of the intervention studies. The objective of these studies was to test the efficiency of an information intervention in terms of information satisfaction, HRQoL, anxiety or depression, while the observational studies searched for a possible relation of information provision and HRQoL, anxiety or depression. Although patients in the experimental conditions overall rated the additional information positive, felt that they received more information, and were satisfied with the overall received information, only one intervention study observed positive relations with HRQoL, anxiety or depression.

Most patients tend to adjust well to their disease and it is therefore possible that additional gains in HRQoL are not easily achieved ³⁰. A further explanation for these results might be the limited surplus value of the additional information given in the experimental conditions. Written information can be useful but is often non-specific and not tailored to patients' information needs, this can lead to confusion or even elevation of anxiety and depression levels ^{31, 41}. Audiotapes seem to facilitate patients' requests to clarify earlier provided information and might enhance the recall of information. Interventions that aim to empower patients might be more useful and effective to decrease anxiety and depression and enhance HRQoL ²³. Mostly, information is given in a neutral mode, with no direct attempt to promote active participation of the patient in the conversation and no attempts to influence patients' inferences. The information provided has an impact on the cognitive level, with no emphasis on affect or the emotions related to the receipt of medical information. The intervention study with a CDROM as decision aid operates both at the cognitive and affective level. Patients who exit their consultation with the belief that they played an active role had better HRQoL scores ²¹. An intervention might therefore be more powerful with elements of counselling or psychotherapy ²⁴.

Another explanation for the lack of intervention effects on HRQoL, anxiety and depression levels may be the short duration of some of the interventions. The information booklet

about chemotherapy was presented for only 30 minutes ²⁴. A recent meta analysis showed that psychosocial interventions should last 12 weeks or more to improve HRQoL ⁴². When the information is offered for a short time it seems reasonable that patients forget a substantive amount of that provided information. Further in six out of eight intervention studies, cancer patients were randomized on individual level, which might result in contamination bias when the health care practitioner gives more than the usual standard information to the control group patients. When this happens, the effects of the experimental conditions might be underestimated. The CDROM study used a quasi-experimental pre-test/post-test design and the PIS study used cluster randomization to overcome the problem of contamination bias and maximize internal validity ^{30, 32, 43}.

In addition, in some of the intervention studies the compliance was low, participants did not use the additional information. For example just below 40% of the patients in the experimental group did not listen to the audiotapes ²¹, and the Italian PIS-study showed that eventually only 48% of the centers indeed started a PIS ³². Results favouring these interventions are therefore difficult to find. When the centers who did not comply with the PIS protocol were removed from the analyses, the intervention did improve patient-centered outcomes ³². The intervention studies show that it is not the quantity but the quality of information that is important for adequate information provision. The addition of general information, with limited surplus value, to the standard information provided did not have an influence on HRQoL or anxiety and depression levels. Instead of adding general information to the standard information provided, the interventions must be directed to give each patient the specific, high quality information they need.

Another important issue is the role of cross-cultural differences in information provision. Truth telling and honest disclosure of cancer information appears to remain controversial in southern and eastern (European) countries ⁴⁴. Awareness of a cancer diagnosis or prognosis is associated with more anxiety and depression, poorer physical, social and emotional QoL in those countries ⁴⁵⁻⁴⁷. However, among the included papers, the association between information provision and HRQoL, anxiety and depression was not different between the different countries.

There are several methodological issues that impede drawing strong conclusions on the relation between information provision and HRQoL. The included studies in this review all used different measures and questionnaires of information provision. There was only one validated information provision questionnaire, the satisfaction with information profile ²⁷. All other studies used subscales of (validated) questionnaires, self-developed and not yet validated questionnaires or single questions. This makes it difficult to compare the results of

the different studies. Only recently the European Organization for Research and Treatment of Cancer (EORTC) developed a questionnaire that evaluates the information received by cancer patients ⁴⁸. It might be helpful to use this validated questionnaire in future studies because it is available in many languages which makes international comparison possible. Also, many different questionnaires are used to assess HRQoL. All these questionnaires claim to assess HRQoL or the individual's perception about their position in life, however many questionnaires measure different constructs and therefore comparison between the studies is difficult. Taken into account these methodological limitations, the overall picture suggests a positive association between information provision and HRQoL.

We can conclude that doctors should provide patients with the information patients desire in order to optimize patient satisfaction. Satisfied patients, patients with fulfilled information needs, and patients who experience less information barriers, in general have a better HRQoL and lower levels of depression and anxiety. The consistency of these associations indicates that further attention must be paid to more patient-centered information provision taking into account the differences in information needs by gender, age, cultural background, educational level, stage of disease and coping style. Additional research is needed to make definitive conclusions about information interventions, as most results did not reach statistical significance due to methodological constraints. The recent emergence of cancer survivorship research and the increasing recognition of its importance will hopefully lead to more research focussing on good information provision interventions that are able to improve HRQoL and decrease psychological distress.

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CHAPTER 5

Illness perceptions in cancer survivors: What is the role of information provision?

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ABSTRACT

Objective: The aim of this study was to provide insight into the relationship between information provision and illness perceptions among cancer survivors.

Methods: All individuals diagnosed with lymphoma, multiple myeloma, endometrial cancer or colorectal cancer between 1998-2008 as registered in the Eindhoven Cancer Registry were eligible for participation. In total, 4446 survivors received a questionnaire including EORTC-QLQ-INFO25 and the Brief Illness Perception Questionnaire; 69% responded (n=3080).

Results: Lymphoma and multiple myeloma patients were most satisfied with the information they received and they perceived to having received more information about their treatment and other services (after care) compared to colorectal and endometrial cancer survivors ($p<0.05$). Multiple myeloma patients reported the highest scores (conceptualized their illness as very serious) on the illness perception scales.

The perceived receipt of more disease-specific information was associated with more personal and treatment control and a better understanding of the illness, while the perceived receipt of more information about other services was associated with more negative consequences of the illness on the patients' life, longer perceived duration of illness, less treatment control, more symptoms attributable to the illness, less understanding of, and stronger emotional reaction to the illness ($p<0.05$). Satisfaction with the received information was associated with better illness perception on all subscales, except for personal control ($p<0.05$).

Conclusion: Improving the patients' illness perceptions by tailoring the information provision to the needs of patients may help patients to get a more coherent understanding of their illness and will possibly lead to a better health-related quality of life.

INTRODUCTION

Health-related quality of life (HRQoL) of cancer patients has been identified as an important endpoint in research and clinical practice. A major determinant of HRQoL, next to the illness itself, is the way patients' perceive and respond to their illness ¹. Research on these illness perceptions is guided by the self-regulation model ². This model is based on the assumption that patients respond to symptoms and signs of illness by forming cognitive and emotional representations of the illness, that lead to coping responses ³. These representations can be divided into eight dimensions: 1. *consequences*, anticipated and experienced consequences of the illness on the patient's life; 2. *timeline*, the perceived progress and duration of the illness; 3. *personal control*, the perception of having self-control and whether the illness is easy to cure; 4. *treatment control*, how much treatment can help to control the illness; 5. *identity*, complaints or symptoms a patient attributes to his/her illness; 6. *illness concern*, worries about illness; 7. *coherence*, how well the patient feels (s)he understands the illness; 8. *emotional representation*, how much patients are emotionally affected by the illness ³. Results of studies among different groups of cancer patients show that negative illness perceptions predicted worse HRQoL and depression after treatment ⁴⁻⁹.

Another important factor associated with HRQoL in cancer patients is adequate information provision ¹⁰. The provision of information to patients is one of the most important factors of supportive cancer care across the whole cancer continuum. Appropriate information provision can result in informed decision making, better treatment adherence, lower levels of distress (anxiety and depression) and higher levels of HRQoL, improved satisfaction with care and sense of control ¹¹⁻¹⁶. However, one of the most frequently reported unmet needs by cancer patients in all phases of the disease is information disclosure (6-93%) ¹⁷, especially the information needs of cancer survivors (post-treatment) are unrecognized ¹⁸. There is a discrepancy between the actual information needs of cancer patients and the perception of health care providers about the needs of these patients ^{16, 19}. A recent study showed that information needs of cancer patients vary as a function of adjustment to cancer ²⁰. The self-regulation model proposes that patients form beliefs about their illness based on abstract and concrete sources of information available to them ⁷. Information provision seems to play an important role in illness perception and HRQoL ¹⁰. However, research into the relationship between information provision and illness perception is lacking. Therefore, the aim of this study was to examine the association between illness perceptions and information provision. We hypothesized that patients who were satisfied with the received information would score better on each illness perception dimension.

METHODS

Setting and Participants

In this study, data from five large population-based cross-sectional surveys on survivors of Hodgkin lymphoma, non-Hodgkin lymphoma, myeloma, endometrial and colorectal cancer was used ²¹. These surveys were set up between 2008 and 2009 using data from the Eindhoven Cancer Registry (ECR), and were designed to evaluate different patient reported outcomes (e.g., late effects, physical and mental health status) among cancer survivors. The data collection procedure across those five surveys was comparable and is described below.

The ECR compiles data of all individuals newly diagnosed with cancer in the southern part of the Netherlands, an area with 10 hospitals serving 2.3 million inhabitants ²². All individuals diagnosed with Hodgkin lymphoma, non-Hodgkin lymphoma or multiple myeloma between 1999 and 2008, or with endometrial cancer or colorectal cancer between 1998 and 2007 as registered in the ECR were eligible for participation. Due to the large number of colorectal cancer survivors (n=5399) a weighted random selection of 2219 patients based on tumour (colon/rectal), sex, and year of diagnosis was made ^{23, 24}. The weights on tumour and sex were derived from the total distribution of colorectal cancer survivors in the ECR region. Patients with shorter years since diagnosis were oversampled for inclusion in future follow-up assessments.

After excluding those patients who had cognitive impairment (medical records and advice attending specialist), had unverifiable addresses, or had died prior to study initiation (according to the ECR, hospital records, and the Central Bureau for Genealogy which collects information on all deceased Dutch citizens via the civil municipal registries), data collection started between 2008 and 2009. All surveys were approved by a local certified Medical Ethics Committee.

Data collection

Survivors were informed of the surveys via a letter from their (ex)-attending specialist. The letter explained that by completing and returning the enclosed questionnaire, patients consented to participate and agreed to the linkage of the questionnaire data with their disease history in the ECR. Patients were reassured that non-participation had no consequences on their follow-up care or treatment. Non-respondents were sent a reminder letter and the questionnaire within 2 months.

Measures

Sociodemographic and clinical characteristics

Data on tumour and patient background characteristics were obtained from the ECR²⁵. The questionnaire contained questions on sociodemographic data, including marital status, current occupation, educational level, and comorbidity. Socioeconomic status was determined by an indicator developed by Statistics Netherlands based on individual fiscal data from the year 2000 on the economic value of the home and household income, and provided as aggregate level for each postal code (average 17 households), which were then categorized into tertiles²⁶. Disease progression (e.g. recurrence, metastasis, or new primary tumour) was determined through check of medical files.

Information provision

To evaluate the information received by cancer survivors, the EORTC QLQ-INFO25 questionnaire was used²⁷. The EORTC QLQ-INFO25 consists of 25 items, grouped into four information provision subscales: perceived receipt of information about the disease (four items regarding diagnosis, spread of disease, cause(s) of disease and whether the disease is under control), medical tests (three items regarding purpose, procedures and results of tests), treatment (six items regarding medical treatment, benefits, side-effects, effects on disease symptoms, social life and sexual activity) and other care services (four items regarding additional help, rehabilitation options, managing illness at home, psychological support). The question format was as follows: “During your current disease or treatment, how much information have you received on?”. In addition, it contains eight single items on receiving written information or information on CDs or tape/video, receiving more or less information, and items on the satisfaction with, amount of, and helpfulness of information. All responses were ranged according to a four-point Likert scale, except for the first four single items which had a binary yes/no scale. All scales were linearly converted to a 0-100 scale, with higher scores indicating better perceived information provision. Internal consistency for all scales is good ($\alpha > 0.70$), as is test–retest reliability (intraclass correlations > 0.70)²⁷.

Illness perceptions

Illness perceptions were assessed using the Brief Illness Perception Questionnaire (B-IPQ), a nine-item instrument used to assess cognitive and emotional representations of the illness²⁸. The English version of the B-IPQ was translated into Dutch by forward-backward translation procedures and adapted for use among cancer patients. The B-IPQ uses a single-item scale approach to assess perceptions on a continuous linear 0-10 point scale. Five of the items assess cognitive illness representations: 1. How much does your illness affect your life (consequences); 2. How long do you think your illness will continue (timeline); 3. How much control do you feel you have over your illness (personal control); 4. How much do you think

your treatment can help your illness (treatment control); 5. How much do you experience symptoms from your illness (identity). Two items assess emotional representations: 6. How concerned are you about your illness (concern) and 7. How much does your illness affect you emotionally (emotional representation). One item assesses illness comprehensibility: 8. How well do you understand your illness (coherence). Answer scales of three items (personal control, treatment control and coherence) were reversed for statistical analyses to get the same response direction as the other five items. A higher score means worse illness perception.

Statistical analyses

Routinely collected data from the ECR on patient and tumour characteristics enabled us to compare the group of respondents, non-respondents and patients with unverifiable addresses, using t-tests for continuous variables and chi-square analyses for categorical variables.

Mean scores on the B-IPQ and EORTC-QLQ-INFO25 for different subgroups were compared using Analyses of Variance (ANOVA) or chi-square analyses for dichotomous items of EORTC-QLQ-INFO25. Multivariate linear regression analyses were carried out in order to investigate the association between the four information provision subscales of the EORTC-QLQ-INFO25 with the B-IPQ items, controlled for demographics and tumour characteristics. Eight linear regression models, respective of the eight single items of the B-IPQ, were estimated with outcomes. Multicollinearity was checked for every analysis. We reran these linear regression analyses stratified by tumour group (endometrial, colorectal, Hodgkin lymphoma, non-Hodgkin lymphoma and multiple myeloma), age group (younger 65, older 65), gender, treatment modality (surgery, radiotherapy, chemotherapy), time since diagnosis (<2 years, >2 years), and comorbidity (none, 1 or >1), based on a priori assumptions that information provision or disease perception may be different among these strata. We tested for effect modification by including cross-product terms in the regression models for variables where stratified analyses showed different results as the main regression models. All statistical tests were two-sided and considered significant if $p < 0.05$. All analyses were conducted using SPSS version 17.0 (Statistical Package for Social Sciences, Chicago, IL, USA).

RESULTS

Patient characteristics

Three thousand and eighty (69.3%) patients returned a completed questionnaire. A comparison of respondents, non-respondents and patients with unverifiable addresses indicated that patients with unverifiable addresses were younger, with more years since diagnosis, and they were less often treated with surgery, and less often diagnosed with colorectal cancer. Non-respondents were more often female, and were less often treated with radiotherapy or chemotherapy²¹.

Sociodemographic and clinical characteristics of cancer survivors, according to type of tumour, are presented in Table 1. Hodgkin lymphoma patients were significantly younger, were more likely to have a job and reported less comorbid conditions than the other four patient groups. Multiple myeloma patients were more recently diagnosed compared to the other four tumour groups. Lymphoma and multiple myeloma patients did not receive surgery as a primary treatment, but significantly more often received chemotherapy and radiotherapy compared to colorectal and endometrial cancer patients.

Table 1: Demographic and clinical characteristics of respondents

	Endometrial cancer (n=742)	Colorectal cancer (n=1352)	Hodgkin lymphoma (n=150)	Non-Hodgkin lymphoma (n=716)	Multiple myeloma (n= 120)	P-value
Age at diagnosis	61.8 ± 8.3	65.0 ± 9.7	41.2 ± 15.4	58.9 ± 12.4	63.0 ± 9.9	<0.01
Age at time of survey	66.7 ± 8.5	69.4 ± 9.6	46.6 ± 15.3	63.7 ± 12.3	66.5 ± 9.4	<0.01
Years since diagnosis	4.9 ± 2.5	4.4 ± 2.5	5.3 ± 2.8	4.8 ± 2.5	3.5 ± 2.3	<0.01
Gender						<0.01
Male	-	765 (56.6%)	81 (54.0%)	439 (61.3%)	64 (53.3%)	
Female	742 (100%)	587 (43.4%)	69 (46.0%)	277 (38.7%)	56 (46.7%)	
Stage at diagnosis						<0.01
I	686 (92.5%)	381 (28.2%)	NA	NA	NA	
II	56 (7.5%)	519 (38.4%)				
III	-	383 (28.3%)				
IV	-	69 (5.1%)				
Treatment						
Surgery	742 (100%)	1341(99.2%)	0 (0%)	0 (0%)	0 (0%)	<0.01
Chemotherapy	8 (1.1%)	364 (26.9%)	145 (96.7%)	436 (61.7%)	91 (75.8%)	<0.01
Radiotherapy	167 (22.5%)	342 (25.3%)	91 (60.7%)	168 (23.8%)	41 (34.2%)	<0.01
Comorbidity						<0.01
None	149 (20.1%)	324 (24.0%)	56 (37.3%)	201 (28.1%)	26 (21.7%)	
1	190 (25.6%)	361 (26.7%)	44 (29.3%)	193 (27.0%)	27 (22.5%)	
>2	403 (54.3%)	667 (49.3%)	50 (33.3%)	322 (45.0%)	67 (55.8%)	
Marital status						<0.01
Married/living together	516 (71.8%)	984 (74.4%)	112 (75.2%)	564 (80.2%)	90 (75.6%)	
Divorced/widowed/ never married	203 (28.2%)	339 (25.6%)	37 (24.8%)	139 (19.8%)	29 (24.4%)	
Educational level						<0.01
University	71 (10%)	254 (19.4%)	13 (8.7%)	111 (15.9%)	23 (19.2%)	
Intermediate school	218 (30.6%)	456 (34.9%)	29 (19.5%)	169 (24.2%)	42 (35.0%)	
Secondary school	249 (34.9%)	322 (24.7%)	59 (39.6%)	253 (36.3%)	33 (27.5%)	
Primary school	175 (24.5%)	274 (21.0%)	48 (32.2%)	164 (23.5%)	22 (18.3%)	
Current occupation						<0.01
Employed	111 (15.5%)	195 (15.0%)	77 (56.6%)	164 (24.4%)	14 (12.1%)	
Not employed	605 (84.5%)	1106 (85.0%)	59 (43.4%)	508 (75.6%)	102 (87.9%)	
Socio-economic status						0.45
Low	164 (22.3%)	290 (22.1%)	29 (20.1%)	146 (20.9%)	25 (21.7%)	
Intermediate	308 (41.9%)	522 (39.7%)	65 (45.1%)	272 (39.0%)	42 (36.5%)	
High	241 (32.8%)	470 (35.7%)	50 (34.7%)	279 (40.0%)	45 (39.1%)	

NA = not available

Table 2. Mean EORTC-INFO-25 subscale scores (\pm SD) according to demographic and clinical characteristics

Satisfaction with information (item INFO25)									
	Information about disease	Information about medical tests	Information about treatment	Information about other services	Satisfaction with information	Usefulness of information	Want more information N (%)	Want less information N (%)	
Tumour									
Not satisfied	37.1(18.0)	47.1(21.6)	27.3(17.9)	10.6(13.3)	-	41.8(22.1)	444(39.4%)	61(5.7%)	
Satisfied	59.0(18.2)**	71.8(19.7)**	50.1(22.9)**	23.7(23.5)**		72.3(20.0)**	190(11.3%)**	32(1.9%)**	
Endometrial									
Colorectal	51.3(22.7)	59.6(26.6)	38.4(24.9)	14.7(18.8)	56.3(26.8)	57.9(25.7)	103(15.3%)	38(5.7%)	
Hodgkin lymphoma	47.7(20.7)	60.8(23.6)	36.9(23.3)	18.1(20.9)	53.4(25.6)	58.1(26.2)	299(23.8%)	34(2.8%)	
Non-Hodgkin lymphoma	56.7(16.2)	68.6(21.4)	56.8(19.0)	26.9(22.0)	66.0(24.7)	73.3(21.7)	42(28.4%)	3(2.1%)	
Myeloma	51.1(20.7)	63.4(22.3)	44.8(22.6)	19.7(22.4)	59.8(26.8)	63.3(24.3)	184(26.4%)	21(3.1%)	
	50.8(23.7)**	65.4(23.5)**	46.5(24.5)**	22.6(21.2)**	58.8(29.2)**	60.9(26.0)**	32(28.3%)**	2(1.9%)**	
Age									
≤ 65	53.2 (20.5)	65.1 (22.2)	46.2 (22.9)	21.1 (21.9)	58.7 (25.9)	63.8 (24.2)	333 (26.3%)	35 (2.8%)	
>65	47.3 (21.4)**	59.1 (25.0)**	36.0 (23.6)**	16.0 (20.1)**	54.7 (26.9)**	57.2 (26.6)**	326 (20.6%)**	63 (4.0%)	
Time since diagnosis									
≤ 2 years	53.3(21.2)	65.3(22.9)	44.8(22.9)	22.1(22.3)	60.5(25.3)	63.9(24.3)	117(24.3%)	17(3.6%)	
>2 years	49.3(21.2)**	61.1(24.1)**	39.8(24.0)**	17.6(20.7)**	55.7(26.7)**	59.4(25.9)**	542(22.5%)	81(3.5%)	
Gender									
Male	49.9 (20.5)	62.7 (22.8)	42.0 (23.5)	19.3 (21.7)	57.9 (26.3)	60.7 (25.7)	346 (26.9%)	34 (2.7%)	
Female	50.0 (21.8)	61.1 (24.9)	39.5 (24.1)	17.6 (20.5)*	55.4 (26.6)**	59.7 (25.7)	314 (19.6%)**	64 (4.1%)*	
Stage at diagnosis									
I	49.9(22.7)	59.4(26.1)	36.3(24.8)	15.2(19.7)	55.6(26.9)	57.6(26.6)	170(17.4%)	46(4.8%)	
II	47.3(20.1)	60.1(23.6)	34.1(22.3)	15.9(19.2)	51.2(24.7)	56.2(25.8)	122(23.0%)	16(3.1%)	
III	49.1(20.0)	62.7(22.0)	43.3(22.7)	22.2(21.9)	55.9(25.0)	60.9(24.7)	86(24.1%)	9(2.6%)	
IV	49.5(21.6)	65.3(23.1)	47.2(19.0)**	19.6(21.9)**	55.2(29.3)**	62.6(25.8)*	24 (35.3%)**	1(1.5%)	
Chemotherapy									
Yes	52.7(19.9)	65.4(22.0)	50.2(21.1)	23.9(22.7)	61.1(25.8)	65.6(25.5)	264(26.1%)	28(2.8%)	
No	49.6(21.4)**	59.8(24.8)**	35.3(23.7)**	15.2(19.5)**	54.1(26.6)**	57.3(26.1)**	392(21.0%)**	70(3.9%)	
Radiotherapy									
Yes	51.1(20.7)	63.7(22.9)	45.4(22.3)	20.1(21.8)	57.7(25.4)	62.9(25.5)	189(24.8%)	21(2.8%)	
No	49.5(21.4)	61.1(24.3)*	38.9(24.2)**	17.7(20.8)**	56.1(26.7)	59.1(25.8)**	467(22.1%)	77(3.8%)	

Table 2. Mean EORTC-INFO-25 subscale scores (\pm SD) according to demographic and clinical characteristics (*Continued*)

	Information about disease	Information about medical tests	Information about treatment	Information about other services	Satisfaction with information	Usefulness of information	Want more information N (%)	Want less information N (%)
Comorbidity								
None	52.9(21.0)	64.5(24.5)	45.3(23.8)	18.6(20.5)	60.9(26.4)	63.1(25.8)	119(17.2%)	29(4.3%)
1	50.0(21.2)	61.8(23.7)	40.7(23.2)	18.4(21.4)	58.6(25.6)	61.5(24.8)	166(21.6%)	17(2.3%)
Two or more	48.6(21.2)**	60.4(23.8)**	38.4(23.9)**	18.2(21.2)	53.2(26.7)**	57.9(25.9)**	375(26.3%)*	52(3.8%)
Marital status								
Married/living together	50.9(20.9)	62.5(23.3)	41.8(23.7)	18.2(21.1)	56.9(26.5)	61.2(25.6)	512(23.7%)	65(3.1%)
Divorced/widowed/never married	47.4(21.9)**	59.7(25.7)**	37.6(24.2)**	19.0(21.0)	55.3(26.3)	57.5(25.8)**	139(20.1%)	28(4.2%)
Educational level								
University	51.9(20.4)	65.5(22.1)	42.4(23.0)	17.8(20.5)	58.1(25.5)	62.4(25.6)	125(27.2%)	13(2.9%)
Intermediate school	50.8(20.4)	62.4(23.5)	40.8(22.2)	17.9(20.5)	56.8(25.8)	61.4(25.3)	200(23.0%)	24(2.8%)
Secondary school	49.4(21.8)	60.6(24.4)	40.7(25.0)	17.8(21.5)	55.7(26.8)	58.5(25.3)	199(22.8%)	26(3.1%)
Primary school	48.5(21.8)*	60.2(25.0)**	39.6(25.2)	20.0(21.7)	56.1(28.0)	59.8(26.6)	122(19.4%)	29(4.8%)
Current Occupation								
Employed	53.7(19.7)	66.2(21.5)	47.7(22.3)	20.8(21.6)	59.5(24.6)	64.4(23.0)	150(27.1%)	13(2.4%)
Not employed	49.0(21.6)**	60.6(24.5)**	38.7(23.8)**	17.4(20.8)**	55.6(27.0)**	59.0(26.2)**	486(21.8%)*	78(3.6%)
Socio-economic status								
Low	50.0(22.6)	59.9(26.3)	40.0(25.2)	18.0(21.1)	54.2(27.6)	57.5(26.4)	136(22.7%)	24(4.2%)
Intermediate	49.5(20.7)	61.4(23.7)	40.5(23.6)	19.0(20.9)	56.6(26.6)	60.0(26.0)	255(22.3%)	38(3.4%)
High	50.7(20.8)	63.8(22.7)**	41.7(23.4)	17.7(20.9)	58.1(25.6)*	61.9(25.0)**	237(23.1%)	32(3.2%)

* < 0.05

** < 0.01

Information provision and satisfaction

Satisfied cancer patients perceived to have received more information (disease, medical tests, treatment and other services) than dissatisfied patients ($p < 0.01$; Table 2). Hodgkin lymphoma cancer patients perceived to have received more information and were more satisfied compared to the other four tumour groups. Non-Hodgkin and multiple myeloma cancer patients perceived to have received more information about treatments than colorectal and endometrial cancer patients ($p < 0.01$). Endometrial cancer patients perceived to have received less information about other services (like options for after care) than the other four tumour groups ($p < 0.01$).

Patients with a advanced stage of the disease at diagnosis (III or IV) were more satisfied with- and perceived to have received more information about treatment and other services ($p < 0.01$) than patients with earlier stage of disease (I and II). Patients who underwent radiotherapy perceived to have received more information about medical tests, treatment and other services, while patients who underwent chemotherapy also perceived to have received more information about the disease and were more satisfied than their counterparts ($p < 0.01$). Patients without comorbidities received more information about the disease, medical tests and treatment and were more satisfied than patients with one or more comorbidities ($p < 0.01$).

Men were more satisfied and wanted to receive more information than women ($p < 0.01$), while women more frequently reported to want less information ($p < 0.05$). Employed patients, patients under 65 years of age, patients with a partner and patients less than two years after diagnosis were more satisfied and scored better on most information provision subscales than their counterparts ($p < 0.01$). Higher educated patients perceived to have received more information about the disease and medical tests than lower educated patients ($p < 0.05$).

Illness perceptions

Endometrial cancer patients experienced less serious consequences and symptoms of their cancer, had shorter timeline beliefs, were less concerned and emotionally affected by their illness compared to the other four tumour groups (all $p < 0.05$; Table 3). Endometrial and Hodgkin lymphoma cancer patients felt to have more personal control over their illness compared to the other three tumour groups, while Hodgkin lymphoma patients also felt their treatment could control their illness more compared to the other groups. Multiple myeloma patients scores highest on all illness perception dimensions, indicating worse illness perceptions. No differences between the cancer types were seen on coherence (understanding) of their illness.

Patients who were not satisfied with the received information, were less than two years after diagnosis, had a higher stage disease, had one or more comorbidities and who received radiotherapy and/or chemotherapy scored worse on most illness perception scales than their counterparts.

Table 3: Mean scores on items of Brief Illness Perception Questionnaire (\pm SD) according to demographic and clinical characteristics

	BIPQ 1 Consequences	BIPQ2 Timeline	BIPQ3 Personal control	BIPQ4 Treatment control	BIPQ5 Identity	BIPQ6 Concern	BIPQ7 Coherence	BIPQ8 Emotional representation
Satisfaction with information								
Not satisfied	4.3(2.6) 3.7(2.5)**	5.1(3.5) 4.6(3.6)**	6.2(3.1) 5.8(3.3)**	4.1(2.8) 3.1(2.5)**	3.8(2.7) 3.4(2.6)**	4.4(2.8) 3.8(2.6)**	4.8(3.1) 3.8(2.9)**	4.0(2.7) 3.3(2.5)**
Satisfied								
Age								
≤ 65	4.3(2.6) 3.7(2.6)**	4.9(3.6) 4.7(3.6)	6.0(3.2) 5.9(3.2)	3.3(2.5) 3.7(2.9)**	3.9(2.7) 3.3(2.6)**	4.3(2.6) 3.8(2.7)**	4.1(2.9) 4.3(3.1)	4.0(2.6) 3.3(2.5)**
>65								
Time since diagnosis								
≤ 2 years	4.5(2.7) 3.9(2.6)**	5.5(3.5) 4.7(3.6)**	6.2(3.1) 5.9(3.2)	3.4(2.5) 3.6(2.8)	3.8(2.7) 3.5(2.6)*	4.7(2.7) 3.9(2.7)	4.3(3.0) 4.2(3.0)**	4.0(2.6) 3.5(2.6)**
>2 years								
Gender								
Male	4.1(2.6) 3.9(2.6)	5.3(3.6) 4.4(3.5)**	6.0(3.2) 5.9(3.3)	3.5(2.6) 3.5(2.8)	3.6(2.6) 3.5(2.7)	4.0(2.7) 4.1(2.7)	4.1(2.9) 4.3(3.1)	3.5(2.5) 3.7(2.6)
Female								
Tumour								
Endometrial	3.2(2.4) 4.1(2.7)	3.1(2.8) 4.5(3.4)	5.6(3.4) 6.1(3.1)	3.4(2.9) 3.8(2.7)	2.9(2.5) 3.6(2.6)	3.6(2.7) 4.2(2.7)	4.3(3.2) 4.3(3.0)	3.3(2.6) 3.6(2.6)
Colorectal	4.1(2.7) 4.3(2.5)	4.5(3.4) 4.0(3.1)	6.1(3.1) 5.6(3.2)	3.8(2.7) 2.3(1.7)	3.6(2.6) 3.8(2.6)	4.2(2.7) 3.9(2.7)	4.3(3.0) 4.0(2.9)	3.6(2.6) 3.9(2.6)
Hodgkin lymphoma	4.1(2.5) 5.5(2.5)**	6.5(3.6) 8.6(2.2)**	6.1(3.3) 6.2(2.9)**	3.4(2.6) 4.1(2.5)**	3.7(2.6) 5.4(2.6)**	4.0(2.7) 5.5(2.7)**	4.2(3.0) 3.9(2.7)	3.7(2.6) 4.4(2.6)**
Non-Hodgkin lymphoma								
Myeloma								
Stage at diagnosis								
I	3.4(2.5) 3.6(2.5)	3.6(3.2) 3.9(3.1)	5.7(3.3) 6.0(3.2)	3.6(2.9) 3.6(2.7)	3.1(2.6) 3.2(2.4)	3.6(2.6) 3.9(2.6)	4.3(3.2) 4.3(3.0)	3.3(2.6) 3.3(2.5)
II								
III	4.7(2.6) 6.4(2.8)**	4.7(3.4) 7.7(2.9)**	6.1(3.0) 6.8(2.8)**	3.6(2.5) 5.0(3.0)**	4.0(2.7) 5.8(2.5)**	4.6(2.7) 6.7(2.7)**	4.3(2.8) 3.7(2.7)	3.9(2.6) 5.5(2.6)**
IV								
Chemotherapy								
Yes	4.6(2.6) 3.6(2.5)**	5.4(3.5) 4.5(3.6)**	6.1(3.1) 5.9(3.3)	3.1(2.3) 3.8(2.9)**	4.1(2.7) 3.3(2.6)**	4.4(2.7) 3.8(2.7)**	4.1(2.8) 4.3(3.1)	4.0(2.6) 3.4(2.5)**
No								

Table 3: Mean scores on items of Brief Illness Perception Questionnaire (\pm SD) according to demographic and clinical characteristics (*Continued*)

	BIPQ1 Consequences	BIPQ2 Timeline	BIPQ3 Personal control	BIPQ4 Treatment control	BIPQ5 Identity	BIPQ6 Concern	BIPQ7 Coherence	BIPQ8 Emotional representation
Radiotherapy								
Yes	4.3(2.6)	5.0(3.5)	5.9(3.1)	3.3(2.5)	4.1(2.7)	4.2(2.7)	4.3(3.0)	3.8(2.6)
No	3.8(2.6)**	4.7(3.6)	6.0(3.3)	3.6(2.8)**	3.4(2.6)**	4.0(2.7)*	4.2(3.0)	3.5(2.6)*
Comorbidity								
None	3.5(2.4)	4.4(3.6)	5.8(3.4)	3.1(2.7)	2.9(2.4)	3.6(2.5)	4.1(3.0)	3.2(2.4)
1	3.7(2.5)	4.6(3.6)	5.8(3.2)	3.3(2.6)	3.3(2.5)	3.9(2.7)	4.2(3.0)	3.4(2.5)
Two or more	4.3(2.7)**	5.2(3.6)**	6.1(3.2)*	3.8(2.8)**	4.0(2.7)**	4.3(2.8)**	4.3(3.0)	3.9(2.7)*
Marital status								
Married/living together	4.0(2.5)	4.8(3.6)	6.0(3.2)	3.5(2.7)	3.6(2.6)	4.1(2.7)	4.2(3.0)	3.6(2.6)
Divorced/widowed/never married	3.9(2.7)	4.8(3.6)	5.8(3.2)	3.7(2.9)*	3.6(2.7)	3.9(2.7)	4.4(3.1)	3.5(2.6)
Educational level								
University	4.1(2.6)	5.2(3.5)	5.9(3.2)	3.5(2.6)	3.6(2.7)	4.0(2.6)	4.1(2.9)	3.5(2.6)
Intermediate school	4.0(2.6)	4.6(3.5)	5.9(3.2)	3.5(2.7)	3.6(2.6)	4.0(2.7)	4.2(3.0)	3.6(2.5)
Secondary school	4.0(2.6)	5.0(3.6)	5.7(3.3)	3.4(2.7)	3.7(2.7)	4.1(2.8)	4.3(3.0)	3.7(2.6)
Primary school	3.8(2.6)	4.7(3.6)**	6.3(3.2)**	3.7(2.9)	3.4(2.6)	4.0(2.8)	4.3(3.1)	3.6(2.6)
Current Occupation								
Employed	4.1(2.5)	4.5(3.5)	5.9(3.2)	3.1(2.4)	3.5(2.5)	4.0(2.5)	4.1(2.8)	3.7(2.5)
Not employed	3.9(2.6)	4.9(3.6)*	6.0(3.2)	3.7(2.8)**	3.6(2.7)	4.0(2.8)	4.3(3.0)	3.6(2.6)
Socio-economic status								
Low	4.2(2.7)	4.9(3.6)	5.9(3.2)	3.7(2.7)	3.7(2.7)	4.4(2.9)	4.5(3.1)	3.9(2.7)
Intermediate	4.0(2.6)	4.7(3.5)	6.0(3.2)	3.4(2.6)	3.6(2.7)	4.0(2.7)	4.3(3.0)	3.6(2.6)
High	3.8(2.5)**	4.8(3.6)	6.0(3.3)	3.5(2.8)	3.4(2.6)	3.9(2.6)**	4.0(2.9)**	3.4(2.5)**

* < 0.05

** < 0.01

Multivariate analyses

Receiving more disease specific information was associated with more personal control and treatment control over the illness, and better understanding of the illness (Table 4). More receipt of information about other services was associated with worse consequences and symptoms of the illness, less treatment control, more concerns and higher emotional impact. Satisfaction with received information was associated with better scores on all illness perception items, except for personal control.

The associations between information about the disease, treatment, other services and illness perceptions were not found in subanalyses among patients less than two years after diagnosis (data not shown). The relation between treatment information and emotional representation was not found for patients who underwent adjuvant chemotherapy and/or radiotherapy (data not shown). The formal tests for interactions between treatment and years since diagnosis with the information subscales only confirmed effect modification for years since diagnosis (data not shown).

Table 4: Standardized betas of multivariate linear regression analyses evaluating the association of independent variables with de BIPQ scales, all patients combined

	BIPQ1 Conse- quences	BIPQ2 Time- line	BIPQ3 Personal control	BIPQ4 Treatment control	BIPQ5 Identity	BIPQ6 Concern	BIPQ7 Coherence	BIPQ8 Emotional representation
Information about disease	0.02	-0.04	-0.11**	-0.10**	0.05	-0.05	-0.12**	0.03
Information about medical tests	0.01	0.03	-0.01	-0.05	-0.02	0.04	-0.03	-0.04
Information about treatment	0.02	-0.01	-0.01	-0.03	-0.04	0.04	-0.04	0.06
Information about other services	0.13**	0.04	-0.04	0.06*	0.13**	0.08**	0.05	0.10**
Satisfaction with information	-0.23**	-0.1**	-0.05	-0.11**	-0.16**	-0.19**	-0.10**	-0.24**

* < 0.05; ** < 0.01; Corrected for gender, age, time since diagnosis, tumour type, treatment, comorbidity, educational level, marital status and current occupation

DISCUSSION

In general, lymphoma and multiple myeloma patients were most satisfied with the received information and perceived to have received more information about their treatment and other services compared to colorectal and endometrial cancer survivors. Multiple myeloma patients reported the worst scores on the illness perception scales, which is in accordance with their disease severity. The perceived receipt of more disease specific information was associated with more control and understanding, while the perceived receipt of more

information about other services was associated with worse illness perceptions. This last finding can be explained by the fact that patients who received more information about other services were the more severely affected patients and therefore had worse illness perceptions. Satisfaction with the received information was the strongest predictor of good illness perceptions.

Our findings are in agreement with the results of a study among head and neck cancer patients⁷. This study found that higher levels of satisfaction with information were related to stronger beliefs in the usefulness of treatment and the controllability of the illness, a better understanding of the illness, and a weaker illness identity, before treatment. However this study only reported correlation coefficients and did not look deeper into the relationship. Another study among six illness groups (without cancer) showed that personal and treatment control and coherence were best in hospitalized myocardial infarction patients, who just received a lot of disease related information, while patients who did not receive a diagnosis reported the worst identity scores, lowest understanding, shortest timeline perceptions, lowest treatment control beliefs and highest emotional response²⁸. Both studies were not specifically focused on the relation between information provision and illness perceptions. In our study we found that time after diagnosis was an effect modifier of the relation between information provision and illness perceptions. Patients diagnosed less than two years ago received more information and had worse illness perceptions; this might indicate that illness perceptions change over time. This finding could also be ascribed to information bias, as the majority of cancer patients receive most information immediately after diagnosis and patients who are more recently diagnosed could therefore better remember the amount of information they received.

Negative illness perceptions were associated with a worse HRQoL, poor adjustment to cancer, depression, treatment adherence and even the perceived benefit from surgery^{6-8, 29, 30}. Besides the association of illness perceptions with HRQoL, adequate information provision and satisfaction with information also have a positive influence on HRQoL, anxiety and depression levels of cancer survivors¹⁰. Our study showed that the illness perceptions were better for patients who were satisfied with the information they received. It is important to gain insight into patients' perceptions of their illness in relation to their satisfaction with information prior to and during treatment⁷ as patients compare the received information with their own ideas and theories of their illness (comparing own current health status with that of past and also health of others) and interpret their disease within this framework^{31, 32}. Inaccurate information provision, misunderstanding, or negative conceptualizations of the illness can all lead to maladaptive responses to the illness. Restructuring illness perceptions by providing appropriate information according to patients' needs, may help patients to

get a more coherent understanding of their illness and will help in a better (long-term) adjustment to cancer ^{1,8}.

Patients differ in the kind and amount of information they require and satisfaction is more related to the extent information needs are met, than to having received all possible information available. The information needs of cancer patients vary by gender, age, cultural background, educational level, cancer type, stage of disease and coping style ^{33, 34}. For example, some patients (monitoring style) search for all kinds of information about their disease, while others (blunting style) distract themselves from information. Patients feel better when the information they receive is tailored to their own coping style ³³. Health care practitioners need to move from a “one size fits all” method of information provision to a more patient centered approach that considers the unique needs, skills, values, illness perceptions, and emotions of patients ³⁵. Research shows that information needs of cancer patients are broader than disease and treatment related information, also encompassing issues of psychosocial well-being which are often not discussed ^{35, 36}. The inclusion of a psychologist into the multidisciplinary oncology team could be helpful to identify maladaptive illness perceptions. Discussing psychosocial items more extensively could help patients interpret the information in the right way ¹. Maladaptive illness perceptions could be changed by giving information meeting patients’ needs, when necessary in combination with an individualized behavioral intervention. Empowerment of patients by teaching them adequate coping skills and self management training will translate into illness perceptions reflecting greater sense of control ³⁷. More research into this area is needed.

The present study has limitations that should be mentioned. Although the response rate was high and information was present concerning demographic and clinical characteristics of the non-respondents and patients of with unverifiable addresses, whether non-respondents declined to participate in the study because of poor health remains unknown. Second, the cross-sectional design of the study limits the determination of causal association between information provision and illness perception, and the change in illness perceptions over time. Different studies found that illness perceptions predicted HRQoL, however a randomized controlled trial showed that patients’ illness perceptions before consultation (uncertainty and negatively emotionally involved) predicted patient satisfaction with the consultation ³⁸. Therefore more research is needed to the direction of this relationship.

In conclusion, we have demonstrated that satisfaction with the received information was the most important factor associated with better illness perception. Improving the patients’ illness perceptions by tailoring the information provision to the needs of patients can possibly lead to a better HRQoL.

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CHAPTER 6

Information provision and patient reported outcomes in patients with metastasized colorectal cancer: results from the PROFILES registry

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ABSTRACT

Background: Patients with metastasized colorectal cancer (mCRC) have different information needs compared to patients with non-metastatic colorectal cancer (CRC). Appropriate information provision leads to better patient reported outcomes for patients with non-metastatic disease.

Objective: To measure the perceived level of, and satisfaction with, information received by patients with mCRC as compared to those with non-metastatic (stage I,II,III) CRC. Also, associations of information provision with health status, anxiety, depression, and illness perceptions were investigated.

Design: A cross-sectional population-based survey was conducted.

Subjects: All CRC patients diagnosed between 2002 and 2007 according to the Eindhoven Cancer Registry were selected. Response was 75% (n=1159; of which 139 had mCRC).

Measurements: Participants completed questionnaires on information provision (EORTC-QLQ-INFO25), health status (SF-36), anxiety and depression (HADS), and illness perceptions (B-IPQ).

Results: The perceived receipt of information was quite comparable between CRC patients with and without mCRC. Only perceived receipt of treatment information was higher for patients with mCRC (45 v. 37; $p < 0.01$). Sixty percent of the patients with mCRC was satisfied with the amount of received information and almost 30% wanted to receive more information. The perceived receipt of more *disease* information and information about *other services* was associated with worse health outcomes, while *satisfaction* with the received information was not associated with health outcomes

Conclusion: The findings of this study indicate that some improvements can be made in the provision of information to patients with mCRC. Adequate assessment of information needs of mCRC patients, as well as appropriate responses to these needs by providing the information in an appropriate way could possibly lead to improvements in patient satisfaction.

INTRODUCTION

The provision of information to patients is one of the most important factors of supportive cancer care. Appropriate information provision can result in informed decision making, better treatment adherence, better health status, lower levels of distress, improved satisfaction with care and a sense of control ¹⁻⁵. However, adequate information provision is a frequently reported unmet need among cancer patients across the whole cancer continuum ⁶. There is a discrepancy between the actual information needs of cancer patients and the perception of health care providers (HCPs) about the needs of cancer patients ^{7, 8}. Most cancer patients want as much information as possible, however this varies by gender, age, cultural background, educational level, coping style and stage of disease ^{5, 9, 10}.

About one fifth of colorectal cancer (CRC) patients will present with metastatic disease, and 20-30% of patients will develop metastatic CRC (mCRC) after successful curative treatment of the primary tumour ¹¹. Patients with mCRC are living longer due to earlier detection and effectiveness of treatments ¹². It is important to ensure patients' well-being during this phase of fighting against a potentially life threatening disease. Patients with mCRC experience decline in health status ¹³, report high levels of anxiety and depression ¹⁴ and have problems with illness perception ¹⁵. Furthermore, they are dealing with specific questions and uncertainties concerning end-of-life issues, symptom relief and patterns of decline ¹⁶. For patients with advanced disease, information about the course of the disease, prognosis, available (palliative) treatment options, how to manage disease symptoms and how cancer will affect daily life are the most important informational needs ¹⁷. Patients need to be aware of the nature of and the course of their disease to make informed medical decisions and to handle and plan this phase of their lives ^{7, 8, 16, 18, 19}. However, a recent study showed that oncologists are often unwilling, unable or uncomfortable to honestly disclose and discuss information regarding diagnosis and prognosis with patients with advanced disease ²⁰. In addition, many HCPs avoid discussing the topic or withhold information ²¹. Furthermore HCPs tend to underestimate patients' need for information and overestimate patients' understanding of their prognosis ⁷.

Since a positive association was found between satisfaction with received information and health outcomes among cancer patients with less advanced disease ^{1, 22}, it is important to study these relations among patients with metastatic disease. Therefore, the objective of this study was to measure the perceived level of, and satisfaction with, information received by patients with mCRC (stage IV) as compared to those with non-metastatic (stage I,II,III) CRC. Second, our objective was to investigate the association of information provision with health status, anxiety, depression, and illness perceptions among patients with mCRC.

METHODS

Setting and participants

This study is part of a long-term follow-up assessment of CRC patients registered with the Eindhoven Cancer Registry (ECR). The ECR compiles data of all individuals newly diagnosed with cancer in southern Netherlands, an area with 10 hospitals serving 2.3 million inhabitants²³. For this study, all patients identified from the ECR and diagnosed with CRC between 2002 and 2007 were eligible for participation. A local certified Medical Ethics Committee approved this study.

Data collection

Data collection started in January 2009 within PROFILES (Patient Reported Outcomes Following Initial treatment and Long term Evaluation of Survivorship). PROFILES is a registry for the study of the physical and psychosocial impact of cancer and its treatment from a dynamic, growing population-based cohort of both short and long-term cancer survivors. PROFILES contains a large web-based component and is linked directly to clinical data from the Eindhoven Cancer Registry (ECR). CRC patients (N=1542) were informed of the study with a letter from their (ex-) attending surgeon. The letter explained that by completing and returning the enclosed questionnaire, patients consented to participate in the study and agreed to the linkage of the questionnaire data with their disease history in the ECR. Details of the data collection method have been previously described²⁴.

Measures

Sociodemographic and clinical characteristics

Patients' sociodemographic and clinical information were available from the ECR. The ECR routinely collects data on tumour characteristics, including date of diagnosis, tumour grade²⁵, clinical stage²⁵, treatment, and patient background characteristics. Since the ECR only collects clinical disease stage at primary diagnosis, we conducted a chart review to identify the respondents who have developed metachronous metastasis between initial diagnosis and the start of our study. Questions on marital status, educational level, current occupation and comorbidity at time of questionnaire were added to the questionnaire.

Information provision

To evaluate the information received by cancer patients, the internationally validated EORTC QLQ-INFO25 questionnaire was used²⁶. The EORTC QLQ-INFO25 consists of 25 items, grouped into four information provision subscales: perceived receipt of information about the disease (four items regarding diagnosis, spread of disease, cause(s) of disease and whether the disease is under control), medical tests (three items regarding purpose, procedures and results of tests), treatment (six items regarding medical treatment, benefits,

side-effects, effects on disease symptoms, social life and sexual activity) and other care services (four items regarding additional help, rehabilitation options, managing illness at home, and psychological support). Additionally, it contains eight single items on for instance wanting to receive more or less information, and on the satisfaction with and helpfulness of the received information. Answer categories range from one (not at all) to four (very much), except for four items with a two point scale (yes/no). After linear transformation, all scales and the items range in scores from 0 to 100, with higher scores indicating better perceived information provision.

Health status

Health status was assessed with the validated Dutch version of the SF-36 questionnaire which incorporates eight domains: physical function, role limitations due to physical health, bodily pain, general health perceptions, vitality, social function, role limitations due to emotional health and general mental health²⁷. According to standard scoring procedures, the subscales were linearly converted to a 0–100 scale, with higher scores indicating better functioning.

Anxiety and depression

Anxiety and depressive symptoms were assessed using the Hospital Anxiety and Depression Scale (HADS). The HADS is a self-report questionnaire comprising 14 items on a four-point Likert-scale; seven for depression and seven for anxiety²⁸. We used a score of eight as a cut-off value for both depression and anxiety^{28, 29}.

Illness perceptions

Illness perceptions were assessed using the Brief Illness Perception Questionnaire (B-IPQ), a nine-item instrument used to assess cognitive and emotional representations of the illness³⁰. The B-IPQ uses a single-item scale approach to assess perceptions on a continuous linear 0-10 point scale. Five of the items assess cognitive illness representations (consequences, timeline, personal control, treatment control and identity), two items assess emotional representations (concern and emotion) and one item assesses illness comprehensibility (coherence).

Statistical analyses

Routinely collected data from the ECR on patient and tumour characteristics enabled us to compare the group of respondents, non-respondents and patients with unverifiable addresses, using ANOVA for continuous variables and chi-square analyses for categorical variables. Furthermore, differences between patients with mCRC and non-metastatic CRC in sociodemographic and clinical characteristics and on the subscales of the EORTC-INFO25, SF-36, HADS and B-IPQ were also analyzed using ANOVA or Wilcoxon tests (when normality and

homogeneity assumptions are violated) for continuous variables and chi-square analyses for categorical variables.

Multivariate linear regression analyses were carried out to investigate the associations of the different information subscales (perceived receipt of disease information, medical test information, treatment information, information about other services and satisfaction with received information) with the subscales of the SF-36, HADS and B-IPQ for patients with mCRC only. We controlled for sociodemographic variables (age, gender) and clinical variables (primary treatment, years since diagnosis and comorbidity).

All statistical tests were two-sided and considered significant if $p < 0.05$. All analyses were conducted using SPSS version 17.0 (Statistical Package for Social Sciences, Chicago, IL, USA).

RESULTS

Patient characteristics

Of the 1542 eligible CRC patients, 1159 (75%) returned a completed questionnaire. A comparison of respondents, non-respondents and patients with unverifiable addresses indicated that respondents and patients with unverifiable addresses were younger and more often male compared to non-respondents (Table 1). No differences were found in mean years after diagnosis, stage of disease and treatment.

Table 1: Demographic and clinical characteristics stratified by response status.

	Respondents (N=1159)	Non-respondents (N=265)	Patients with unverifiable addresses (N=118)	P-value
Mean age at time of survey (SD)	69.2 (9.7)	71.1 (10.2)	68.3 (11.4)	0.008
Mean years since diagnosis (SD)	3.5 (1.5)	3.6 (1.6)	3.7 (1.5)	0.530
Gender				0.003
Male	663 (57.2%)	121 (45.7%)	63 (53.4%)	
Female	496 (42.8%)	144 (54.3%)	55 (46.6%)	
Stage at diagnosis*				0.507
I	309 (26.7%)	71 (26.8%)	33 (28.0%)	
II	450 (38.8%)	108 (40.8%)	47 (39.8%)	
III	331 (28.6%)	78 (29.4%)	29 (24.6%)	
IV	69 (6.0%)	8 (3.0%)	9 (7.6%)	
Primary treatment				0.253
SU only	599 (51.7%)	162 (61.6%)	64 (54.2%)	
SU + RT	231 (19.9%)	38 (14.4%)	21 (17.8%)	
SU + CT	250 (21.6%)	48 (18.3%)	23 (19.5%)	
SU + RT + CT	68 (5.9%)	12 (4.6%)	9 (7.6%)	
CT only	11 (0.9%)	3 (1.1%)	1 (0.8%)	

*Disease stage at primary diagnosis

SU = surgery; RT = radiotherapy; CT = chemotherapy

Patients with mCRC were significantly younger, were more recently diagnosed, were more often men, had a higher socioeconomic status and more often received chemotherapy (in addition to surgery) as primary treatment compared to patients without metastasis (Table 2). No differences were found in the number of comorbidities, marital status, educational level and employment between these two groups.

Table 2: Demographic and clinical characteristics of respondents stratified by stage of the disease

	Patients with metastasis at time of study (N=139)	Patients without metastasis at time of study (N=1020)	P-value
Mean age at time of diagnosis (SD)	62.7 (9.2)	66.1 (9.7)	<0.001
Mean age at time of survey (SD)	65.9 (9.2)	69.7 (9.7)	<0.001
Mean years since initial diagnosis (SD)	3.2 (1.3)	3.6 (1.5)	0.01
Median years since diagnosis (25-75%)	2.9 (2.2-4.0)	3.2 (2.4-4.5)	
Gender			0.02
Male	92 (66.2%)	571 (56.0%)	
Female	47 (33.8%)	449 (44.0%)	
Primary treatment			<0.001
SU only	38 (27.3%)	561 (55.0%)	
SU + RT	17 (12.2%)	214 (21.0%)	
SU + CT	61 (43.9%)	189 (18.5%)	
SU + RT + CT	12 (8.6%)	56 (5.5%)	
CT only	11 (7.9%)	-	
Comorbidity			0.92
None	34 (24.5%)	255 (25.0%)	
One	35 (25.2%)	270 (26.5%)	
Two or more	70 (50.4%)	495 (48.5%)	
Marital status			0.14
Partner	108 (80.6%)	733 (74.3%)	
No partner (single/divorced/widowed)	26 (19.4%)	254 (25.7%)	
Educational level			0.50
High	190 (19.5%)	24 (18.0%)	
Medium	336 (58.4%)	86 (64.6%)	
Low	215 (22.1%)	23 (17.3%)	
Employment status			0.90
Not working	112 (84.2%)	824 (84.6%)	
Working	21 (15.8%)	150 (15.4%)	
Socioeconomic status			0.04
Low	22 (16.8%)	222 (23.1%)	
Medium	49 (37.4%)	402 (41.9%)	
High	60 (45.8%)	336 (35.0%)	

SU = surgery; RT = radiotherapy; CT = chemotherapy

Education levels included low: no/primary school, medium: lower general secondary education/vocational training, or high: pre-university education/high vocational training/university.

Table 3: Information provision, health status, anxiety and depression and illness perceptions stratified by stage of the disease (mean (SD))

	Patients with metastasis at time of study (N=139)	Patients without metastasis at time of diagnosis study (N=1020)	P-value
Information provision*			
Information about the disease	49.7 (21.2)	48.2 (20.4)	0.44
Information about medical tests	64.6 (21.9)	61.4 (23.3)	0.14
Information about treatments	45.2 (19.8)	36.6 (23.4)	<0.01
Information about other services	19.9 (21.9)	19.0 (21.1)	0.65
Satisfaction with information	55.2 (26.3)	53.9 (25.7)	0.60
Usefulness of information	62.0 (26.0)	58.7 (26.1)	0.18
Want more information N(%)	38 (28.6%)	220 (23.5%)	0.20
Want less information N(%)	2 (1.5%)	27 (3.0%)	0.57
Health status (SF36)**			
General Health	44.4 (24.3)	63.6 (21.0)	<0.01
Physical Functioning	60.7 (30.8)	70.1 (27.2)	<0.01
Role Limitations Physical Health	44.3 (43.9)	66.4 (41.9)	<0.01
Bodily Pain	70.6 (28.6)	76.9 (24.2)	<0.01
Vitality	58.4 (23.1)	65.9 (20.4)	<0.01
Social Functioning	71.8 (27.4)	82.2 (21.0)	<0.01
Role Limitations Emotional Problems	70.9 (41.3)	81.9 (34.7)	<0.01
Mental Health	75.0 (18.0)	77.7 (17.3)	0.09
Anxiety ***	5.5 (4.2)	4.7 (3.7)	0.02
Anxiety dichotomized#			0.09
0-7 N(%)	95 (72.5%)	759 (79.3%)	
8-21 N(%)	36 (27.5%)	198 (20.7%)	
Depression ***	5.6 (3.5)	5.2 (3.5)	0.24
Depression dichotomized#			0.27
0-7 N(%)	91 (71.7%)	722 (76.4%)	
8-21 N(%)	36 (28.3%)	223 (23.6%)	
Illness perceptions****			
1 Consequences	6.1 (2.8)	4.0 (2.5)	<0.01
2 Timeline	7.6 (2.8)	4.2 (3.3)	<0.01
3 Personal control	6.8 (2.9)	6.0 (3.1)	<0.01
4 Treatment control	5.1 (2.8)	3.5 (2.6)	<0.01
5 Identity	5.0 (2.6)	3.5 (2.6)	<0.01
6 Concern	6.5 (2.7)	4.0 (2.5)	<0.01
7 Coherence	3.7 (2.9)	4.4 (3.0)	0.01
8 Emotional representation	5.0 (2.7)	3.6 (2.5)	<0.01

+ Higher score indicates more perceived receipt of information

++ Higher score indicates better functioning;

+++ Higher score indicates higher levels of anxiety/depression;

++++ Higher score indicates worse illness perceptions

Based on their sum score, participants can be divided over two categories (<8 no anxiety/depression; ≥8 anxiety/depression)^{28, 29}

Information provision and satisfaction: differences between patients with non-metastatic and mCRC

On the subscales of the EORTC-QLQ-INFO25, patients with mCRC indicated to having received more information compared to patients with non-mCRC. However this was only significant for the subscale information about treatments (Table 3).

In-depth analyses of single items of the EORTC-QLQ-INFO25 showed comparable results between both groups, where 72% of the cancer patients with mCRC received (quite) a lot information about their diagnosis (versus 66% of the patients without metastasis). Seventeen percent (vs. 15%) received (quite) a lot information about the causes of their disease. The perceived receipt of medical test information was high: 73% (vs. 64%) received (quite) a lot information about the goals of the tests, 74% (vs. 68%) about the course of the tests and 79% (vs. 74%) received information on the results of the tests. Most patients with mCRC received (quite) a lot treatment information (80% vs. 64%), about the results of the treatment (51% vs. 47%) and about the side effects of treatments (65% vs. 35%). In contrast, a lot less information was received on other services, for example rehabilitation options (14% vs. 13%), dealing with cancer at home (21% vs 20%) and psychological help (12% vs. 7%).

There were no significant differences between the two groups on satisfaction with and usefulness of the received information (Table 3). More than half (60% vs. 55%) of the patients with metastasis was (quite) satisfied with the received information and 68% (vs. 63%) perceived the received information as (quite) useful. Patients with mCRC wanted to receive more information (29% vs. 24%), especially about the course of the disease (prognosis, future), side effects of treatment(s) and supportive care (open field question).

Health status, anxiety and depression, illness perception: differences between patients with metastatic and non-metastatic CRC

Patients with mCRC reported worse health status except for mental health (all $p < 0.01$), higher levels of anxiety ($p = 0.02$) and quite similar levels of depression ($p = 0.24$) (Table 3). Patients with mCRC perceived their illness as worse (belief that their life is more affected, their disease is of longer duration, have less treatment and personal control, more symptoms, and were more concerned and emotionally affected) compared to patients without metastasis, which is in accordance with their disease severity (all $p < 0.01$). Patients with mCRC had a better understanding of their illness compared to patients without mCRC ($p = 0.01$). No differences in health outcomes were found between patients with synchronous ($n = 69$) and metachronous metastasis ($n = 70$; data not shown).

Association of information provision and information satisfaction with health status, anxiety and depression, and illness perceptions among CRC patients with mCRC

Among patients with mCRC more information about the *disease* was associated with worse general health, social functioning and bodily pain, while more information about the *treatment* was associated with less role limitations due to emotional problems when corrected for covariates (Table 4). More information about *other services* was associated with worse functioning on all domains (except social functioning and general health), higher levels of depression and more symptoms attributed to their illness.

Among patients without metastatic disease, higher *satisfaction* with the received information was associated with better health status, lower levels of anxiety and depression and better illness perceptions, whereas more perceived receipt of information about *other services* was negatively associated with these outcomes (data not shown).

DISCUSSION

The present study showed that the perceived receipt of information was quite comparable between patients with and without mCRC. Patients with mCRC perceived receiving more treatment-related information compared to patients with non-mCRC. However, both groups perceived having received little information about other services and indicated to want more information. Issues related to disease course and supportive care were mentioned most frequently as topics that patients with mCRC wanted to receive more information about. Only 60% of the patients with mCRC was (quite) satisfied with the received information.

Despite the severity of their disease, the majority of cancer patients with metastasis want to be fully informed³¹. However, 40% of the patients with mCRC in our study was not satisfied with the received information and almost 30% wanted to receive more information. This possibly indicates that not all informational needs were met. This is confirmed by our finding that patients with mCRC reported receiving only a little information about other services, and wanted more information about these topics. Other studies showed that the perceived need for additional help was very high among advanced cancer patients, but HCPs are often unaware of this need³². HCPs are inclined to give routine medical/technical information (diagnosis, type of treatment) and avoid emotional and quality of life issues³³. Furthermore, patients with mCRC possibly want (and expect) more direct emotional support from their HCP instead of only a referral to more formal organized support³².

Table 4: Standardized betas of multivariate linear regression analyses evaluating the association of information provision subscales with health status, anxiety and depression, and illness perceptions (these analyses only include patients with metastasized disease at time of diagnosis)

	Information about the disease	Information about medical tests	Information about treatment	Information about other services	Satisfaction with information
Health status+					
General Health	-0.24*	ns	ns	ns	ns
Physical Functioning	ns	ns	ns	-0.36**	ns
Role Limitations Physical Health	ns	ns	0.32*	-0.32**	ns
Bodily Pain	-0.24*	ns	ns	-0.26*	ns
Vitality	ns	ns	ns	-0.37*	ns
Social Functioning	-0.26*	ns	ns	ns	ns
Role Limitations Emotional	ns	ns	ns	-0.25*	ns
Mental Health	ns	ns	ns	-0.32**	ns
Anxiety and depression#					
Anxiety	ns	ns	ns	ns	ns
Depression	ns	ns	ns	0.29**	ns
Illness perceptions^					
1 Consequences	ns	ns	ns	ns	ns
2 Timeline	ns	ns	ns	ns	ns
3 Personal control	ns	ns	ns	ns	ns
4 Treatment control	ns	ns	ns	ns	ns
5 Identity	ns	ns	ns	0.27*	ns
6 Concern	ns	ns	ns	ns	ns
7 Coherence	ns	ns	ns	ns	ns
8 Emotional representation	ns	ns	ns	ns	ns

** < 0.01; * < 0.05; ns = not significant

Corrected for gender, age, time since diagnosis, chemotherapy and comorbidity

+ Higher score indicates better functioning; # Higher score indicates higher levels of anxiety/depression; ^Higher score indicates worse illness perceptions

Our results do not show differences in the perceived level of received information between patients with or without mCRC. This could indicate that the information HCPs provide is very general and routinely given, and not tailored to the individual patient. Further complicating the interpretation of our results is that cancer patients tend to forget a substantial amount of information that has been given to them, because they may be emotionally overwhelmed³⁴, impaired in their cognitive capability, may not understand the medical terminology used, or in the case of metastasized disease deny the “terminal” nature of their illness as a coping strategy to retain hope^{16, 35}. HCPs may have provided the required information but patients do not recall having received this information. Since satisfaction with information provision is for a part determined by the amount of information received, it is important that HCPs constantly check what the patient has understood and whether the information was helpful³⁶.

When necessary, the HCP must repeat the information several times, both between and within consultations ⁷.

The perceived receipt of more *disease* information and information about *other services* was associated with worse health outcomes among patients with mCRC. Part of this result could be influenced by confounding. Information provision about metastasis and *other services* may cause negative feelings on its own, since it is often emotionally loaded, while information about *treatment* options possibly gives the patient new hope. Hope is an important factor for a person's well-being and quality of life ³⁷. Also, treatment information could empower the patient to anticipate and react to expected toxicities with a clear action plan. Furthermore, information provision about *other services* was too limited for most patients, possibly leading to more uncertainty or confusion.

While satisfaction with the received information was associated with better health outcomes among patients with curable cancer ¹, we did not find this association in our study among patients with mCRC. A possible explanation for the absence of this association is that next to the amount of information, the content of information and the way the information is provided are at least equally important for the satisfaction levels of patients with mCRC ³⁸. Furthermore, patient satisfaction is associated with supportive HCP behaviors ³³, the way information is provided (although not assessed in this study) could influence the way information will be perceived ¹⁶. Advanced cancer patients want the HCP to be honest, to convey hope, to speak plain language instead of difficult medical terminology, to be empathic, to give enough time during discussion and to pace the amount of information to what they can assimilate ¹⁶. Another study reported that 100% of the respondents wanted HCPs to be honest, while 91% also wanted HCPs to be optimistic. However, it is difficult for HCPs to remain optimistic while being honest about a poor prognosis ³⁹.

Further, our results showed that patients with mCRC had worse illness perceptions compared to CRC patients without metastasis. Patients with mCRC were aware of the severity of their disease and also reported a better understanding of their illness compared to patients without mCRC. This indicates that HCPs did a good job in informing patients about their disease severity. However, we did not find an association between information provision and illness perceptions for patients with mCRC. In comparison, a recent study showed that patient awareness of incurable disease was associated with improvements in health status ⁴⁰, since they were better able to understand and manage their symptoms.

Our results indicate that the delivery of information to patients with mCRC can be improved. Adequate assessment of patients' individual information needs as well as appropriate responses to these needs might lead to higher levels of satisfaction. HCPs can start a

conversation by giving general information per topic and then ask whether or not a patient want to discuss this topic in more detail ⁴¹. In particular, providing information about other services can be bettered as both metastatic and non-mCRC survivors perceived receiving little information on this topic. HCPs need to become aware of the supportive care needs and provide the patient with more emotional and quality of life information when necessary. However, HCPs might not feel competent to provide patients with information about advanced disease ⁴². Since satisfaction levels of mCRC patients might not only be related to the amount of information received, but also to the way the information is provided it seems important to pay attention to the communication skills of HCPs by developing and implementing education and training programs ⁴³.

The study has limitations. First, patients with mCRC included in our study were long-term survivors which could have biased our results. Relative survival for stage IV colon and rectal cancer was respectively 7% and 6% in the period 2004-2006 ⁴⁴. Multi-agent chemotherapy has enabled previously unresectable mCRCs to be resected ¹¹ and five-year relative survival for patients undergoing hepatic resection has increased to 45% ⁴⁵. It is therefore possible that part of the patients with mCRC were cured at time of our study. Since we aimed to compare the levels of received information between patients who are curable (non-mCRC) and those who are incurable (mCRC), the potential curability of mCRC could have confounded our results. Unfortunately, we did not have data about the exact rates of cure in our study sample. Future research is needed to determine differences over time in health outcomes between patients with mCRC who are actually cured and those with incurable mCRC. Second, the cross-sectional design of the study limits the determination of causal associations between information provision and health outcomes. Third, since all participants were CRC patients, we can only generalize our results to this group of cancer patients. Finally, the EORTC QLQ-INFO25 does not measure who provided the information and when the information was provided exactly. It would be interesting to assess which aspects of information patients receive from different HCPs or other sources and at what point in their disease trajectory they receive the information. Prospective research is needed to overcome part of the recall bias.

In conclusion, the findings of this study indicate that some improvements can be made in the provision of information to patients with mCRC. Patients especially wanted more information about supportive care. Our results with regard to the associations between perceived receipt of more *disease* information and information about *other services* with worse health outcomes should be interpreted with care, since the way and the content of the information provided are probably more important for patient satisfaction than the amount of received information. This can possibly also explain the lack of a relation between satisfaction with the received information and health outcomes.

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CHAPTER 7

Satisfaction with information is associated with baseline and follow-up quality of life among lymphoma and multiple myeloma survivors: results from the PROFILES registry

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Submitted

ABSTRACT

Background: Providing information that is congruent with patients' needs is an important determinant for patient satisfaction and might also affect health-related quality of life (HRQoL), anxiety and depression levels of cancer survivors.

Aim: To obtain insight into the relationship between information provision and HRQoL, anxiety and depression levels among lymphoma and Multiple Myeloma (MM) survivors.

Methods: All patients diagnosed with lymphoma or MM between 1999 and 2009, registered in the Eindhoven Cancer Registry, received a questionnaire including the EORTC QLQ-INFO25, EORTC QLQ-C30 and HADS. Subsequently, 407 of the 1369 participants completed these questionnaires again two years later. Paired sample t-tests were used to assess changes over time and multivariate linear regression analyses were used to determine independent associations of information provision with HRQoL, levels of anxiety and depression.

Results: The perceived receipt of information about *medical tests* (65 vs. 62, $p < 0.01$), *treatment* (48 vs. 45, $p = 0.01$) and the helpfulness of the received information (66 vs. 63, $p = 0.04$) were significantly higher at baseline compared to 2-year follow-up. The perceived level of information about the *disease* and *other services* and the HRQoL and levels of anxiety and depression did not change over time.

Higher *satisfaction* with the received information at T1 was associated with better physical, role, emotional and social functioning and global quality of life at T2 (β ranging from 0.15 – 0.25; all $p < 0.05$). After correction for baseline functioning levels, this relationships remained only significant for role functioning ($\beta = 0.17$, $p < 0.05$) and global quality of life ($\beta = 0.14$, $p < 0.05$). Survivors who were satisfied at both time points (56%) reported highest levels of mental HRQoL.

Discussion: Satisfaction with the received information is associated with better HRQoL and lower levels of anxiety and depression. Survivors, who are stable satisfied with information, report better mental HRQoL. Future studies should explore strategies to optimize patient satisfaction with received information.

INTRODUCTION

The provision of information to patients is one of the most important factors of cancer care across the cancer continuum. The goal of providing information is to prepare patients for their treatment, to increase treatment adherence and abilities to cope with the illness as well as to promote recovery ¹. Adequate information provision is a difficult task since information is often complex, meant to make serious decisions, and potentially upsetting ². The majority of cancer patients (>80%) want as much information as possible about their disease, treatment and rehabilitation ³⁻⁵. Information preferences vary by sex, age, cultural background, time since diagnosis, educational level, stage of the disease and coping style ⁶⁻⁸. Results of a systematic review show that 6-93% of the cancer patients report adequate information provision as an unmet need ⁹, indicating the existence of misconceptions among health care providers (HCP) regarding patients' needs for information ¹⁰.

A study among lymphoma and multiple myeloma (MM) survivors showed that information provision and satisfaction with the received information were relatively good, however one third of patients still expressed unmet information needs ¹¹. A recent review from our group showed that satisfied patients and patients with fulfilled information needs in general have a better health-related quality of life (HRQoL) and lower levels of anxiety and depression ¹². However, most studies included in this review were inconclusive because of methodological flaws. Almost all included studies used non-validated questionnaires to measure information provision, sample sizes were small, and most studies had a cross-sectional design which limits the determination of causal associations. Therefore, the aim of the current study was to examine the relationship between information provision at baseline and HRQoL, anxiety and depression among lymphoma and MM survivors 2 years later.

METHODS

Setting and population

This study is part of a dynamic longitudinal population-based survey among lymphoma and MM survivors registered within the Eindhoven Cancer Registry (ECR) of the Comprehensive Cancer Centre South. The ECR records data on all patients who are newly diagnosed with cancer in the southern part of the Netherlands, an area with 2.3 million inhabitants, 18 hospital locations and 2 large radiotherapy institutes. The ECR was used to select all patients who were diagnosed with non-Hodgkin lymphoma (NHL), Hodgkin lymphoma (HL) and MM between 1/1/1999 and 1/1/2009. We included indolent (including Chronic Lymphocytic Leukemia) and aggressive B-cell NHL, HL, and MM as defined by the International Classification of Diseases for Oncology-3 codes (ICD-O-3)¹³. Ethical approval for the study was obtained from a local certified Medical Ethics Committee.

Data collection

Data collection was done within PROFILES (Patient Reported Outcomes Following Initial treatment and Long term Evaluation of Survivorship). PROFILES is a registry for the study of the physical and psychosocial impact of cancer and its treatment from a dynamic, growing population-based cohort of both short and long-term cancer survivors. PROFILES contains a large web-based component and is linked directly to clinical data from the ECR. Details of the data collection method were previously described ¹⁴. From May until November 2009, patients between 6 months and 10 years after diagnoses were included in the study and received the first questionnaire at baseline (T1). From May until November 2011, the patients who agreed to participate in the follow-up received the second questionnaire containing the same study measures (T2).

Study measures

Socio-demographic and clinical characteristics

Clinical information was available from the ECR that routinely collects data on tumour characteristics, including date of diagnosis, tumour grade, histology, stage ¹⁵, primary treatment, and patients background characteristics, including sex and date of birth. Comorbidity at the time of survey was categorized according to the adapted Self-administered Comorbidity Questionnaire (SCQ) ¹⁶. Questions on marital status, educational level, and current occupation were added to the questionnaire.

EORTC QLQ-INFO25

The Dutch version of the internationally validated European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Information (EORTC QLQ-INFO25) was used to evaluate the information received by lymphoma and MM patients ^{17 18}. This 25-item questionnaire incorporates four information provision subscales: perceived receipt of information about the *disease* (four items regarding diagnosis, spread of disease, cause(s) of disease and whether the disease is under control), *medical tests* (three items regarding purpose, procedures and results of tests), *treatment* (six items regarding medical treatment, benefits, side-effects, effects on disease symptoms, social life and sexual activity) and *other care services* (four items regarding additional help, rehabilitation options, managing illness at home, psychological support). Additionally, it contains eight single items on for instance wanting to receive more or less information, and on the satisfaction with and helpfulness of the received information. Answer categories range from one (not at all) to four (very much), except for four items with a two point scale (yes/no). After linear transformation, all scales and the items range in scores from 0 to 100, with higher scores indicating better perceived information provision.

EORTC QLQ-C30

HRQoL was measured by the Dutch version of the validated EORTC QLQ-C30¹⁹. This 30-item HRQoL questionnaire consists of five functional scales (physical, role, cognitive, emotional and social), a global health status quality of life scale and three symptom scales and single symptom items. Answer categories range from one (not at all) to four (very much). After linear transformation, all scales and single item measures range in score from 0 to 100²⁰. A higher score on function scales and global quality of life implies better HRQoL.

Anxiety and depression

Anxiety and depressive symptoms were assessed using the Hospital Anxiety and Depression Scale (HADS). The HADS is a self-report questionnaire comprising 14 items on a four-point Likert-scale; seven for depression and seven for anxiety²¹. The depression subscale mainly covers loss of interest and pleasure (anhedonia), which are core depressive symptoms, while the anxiety subscale covers the core anxiety features of worry and tenseness. The scores range from 0-21, with higher scores indicating higher levels of anxiety or depression. A cut-off score of 8 was used to determine symptoms of depression or anxiety^{21, 22}.

Statistical analyses

Differences in socio-demographic and clinical characteristics between respondents and non-respondents or patients with unverifiable addresses and patients who completed one or two questionnaires were compared with a chi-square or t-test, where appropriate.

Paired sample t-tests were performed to compare the mean EORTC QLQ-INFO25, EORTC QLQ-C30 and HADS scores on T1 and T2. The same analyses were performed for the subgroup of short-term survivors (<2 years since diagnosis at baseline) only.

The mean scores on the EORTC QLQ-C30 functioning and HADS scales on T1 and T2, stratified by the score on the satisfaction with received information question of the EORTC QLQ-INFO25 1) unsatisfied, 2) a little satisfied, 3) quite satisfied, 4) very satisfied, were compared by ANOVA.

Multivariate linear regression analyses were carried out in order to investigate the association on T1 between HRQoL, anxiety and depression (dependent variables) with the four information provision subscales and satisfaction with received information (independent variables), controlled for covariates age, sex educational level, marital status, time since diagnosis, tumour type, disease stage and number of comorbidities, that were determined a priori²³.

Furthermore, the predictive value of the four information provision subscales and satisfaction with received information (T1) on HRQoL, anxiety and depression (T2) was investigated by multivariate linear regression analyses corrected for baseline HRQoL, anxiety and depression

(T1) and the same covariates as described above. These analyses were also performed for the subgroup of short-term (<2 years since diagnosis at baseline) only.

Additionally, mean EORTC QLQ-C30 subscale scores, stratified by survivors who were 1) satisfied at T1 and T2 (stable satisfied), 2) unsatisfied at T1 and satisfied at T2 (became satisfied), 3) satisfied at T1 and unsatisfied at T2 (became unsatisfied) 4) unsatisfied at T1 and T2 (stable unsatisfied), were compared by ANOVA. Multivariate linear regression analyses were carried out, to investigate the association between the stability of satisfaction with received information (independent) with HRQoL, anxiety and depression (dependent), corrected for baseline HRQoL, anxiety and depression and the same covariates as described above.

All statistical tests were two-sided and considered significant if $p < 0.05$. All analyses were conducted using SPSS version 17.0 (Statistical Package for Social Sciences, Chicago, IL, USA).

RESULTS

Patient characteristics

Of the 2,033 lymphoma and MM survivors who were sent a questionnaire, 1,369 (67%) completed this. Subsequently, 407 (30%) completed this questionnaire again two years later. Patients with unverifiable addresses were younger and diagnosed longer ago compared to respondents and non-respondents (Table 1). Non-respondents were more often diagnosed with MM, less often with aggressive NHL, disease stage was more often unknown, and they received chemotherapy less often but active surveillance more often compared to respondents.

The mean age at baseline survey completion was 61.6 years with a mean time since diagnosis of 3.8 years (Table 1). Chemotherapy was the most common primary treatment (66%). Two third of the survivors reported one or more comorbid conditions; most common were arthritis, back pain and hypertension.

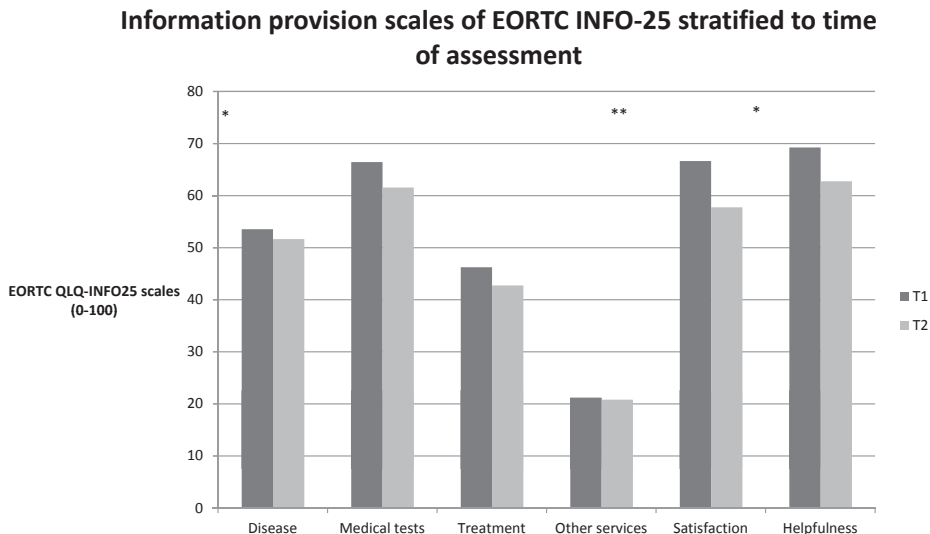
A baseline comparison between survivors who completed one or two questionnaires indicated that the latter had a significant longer mean time since diagnosis, more often received stem cell transplantation, were employed and had a partner more often (Table 1). Furthermore, survivors who completed both questionnaires scored somewhat better on physical and emotional functioning, global quality of life and had lower levels of anxiety and depression compared to survivors who only completed the baseline questionnaire (Table 2), although differences were not clinically relevant ²⁴.

Changes over time in information provision, HRQoL, anxiety and depression

The perceived receipt of information about *medical tests* (65 vs. 62, $p<0.01$) and *treatment* (48 vs. 45, $p=0.01$) and the usefulness of the received information (66 vs. 63, $p=0.04$) were significantly higher at T1 compared to T2 for the total group of survivors (Table 2). Survivors <2 years since diagnosis showed a significant decrease in *medical test* information and *satisfaction* with and *helpfulness* of the received information (Figure 1).

In total, 28% of the survivors would have liked to receive more information at T1 and 23% at T2. Most frequently mentioned topics to receive more information about were the possible causes of cancer, possible side-effects of their treatment, long-term effects of cancer on different aspects of life, aftercare, and overall information on cancer. Overall, 22% of the survivors wanted to receive more information at one of the assessment periods, 63% wanted no additional information and 15% did want to receive more information at both assessment periods. Of this latter group, 47% wanted to receive information about the same topics and 53% wanted to receive different information at T2 compared to T1 (from more general disease specific information to information about the course of the disease and aftercare).

Figure 1: Differences in perceived level of information received and satisfaction with and usefulness of information over time for survivors <2 years since diagnosis.



* $p<0.05$; ** $p<0.01$; T1 = assessment one; T2 = assessment two

Table 1: Socio-demographic and clinical characteristics of questionnaire respondents, non-respondents and patients with unverifiable addresses.

Respondents			Non-respondents	Patients with unverifiable addresses	P-value	Respondents who completed one questionnaire vs. two questionnaires	Respondents vs. non-respondents vs. patients with unverifiable addresses
N= 1369	Survivors who completed both questionnaires N= 407	N= 364	N= 300				
Tumour type							
I-NHL	547 (40%)	155 (38%)	157 (43%)	121 (40%)	0.58		<0.01
A-NHL	454 (33%)	138 (34%)	89 (25%)	85 (28%)			
HL	185 (14%)	62 (15%)	40 (12%)	52 (17%)			
MM	182 (13%)	52 (13%)	78 (21%)	42 (14%)			
Age (at T1) (mean ± SD)	61.6 (14.1)	61.2 (12.8)	62.2 (15.4)	57.5 (16.2)	0.58		<0.01
<55	377 (28%)	103 (25%)	106 (29%)	125 (42%)	<0.01	<0.01	
55-69	536 (39%)	193 (47%)	110 (30%)	85 (28%)			
≥ 70	453 (33%)	111 (27%)	148 (41%)	90 (30%)			
Years since diagnosis (mean ± SD)	3.8 (2.6)	4.3 (2.7)	3.5 (2.8)	4.2 (2.8)	<0.01	<0.01	0.006
<2 years	455 (33%)	102 (25%)	154 (42%)	84 (28%)	<0.01	<0.01	<0.01
2-4	514 (38%)	156 (38%)	119 (33%)	118 (39%)	0.48		0.11
5-7	263 (19%)	100 (25%)	46 (13%)	56 (19%)			
8-10	136 (10%)	49 (12%)	45 (12%)	42 (14%)			
Sex					0.11		<0.01
Male	794 (61%)	253 (62%)	197 (56%)	161 (56%)			
Female	509 (39%)	153 (38%)	153 (44%)	129 (45%)			
Stage at diagnosis							
I	287 (21%)	80 (20%)	59 (16%)	67 (22%)	0.11		<0.01
II	255 (19%)	91 (22%)	62 (17%)	43 (14%)			
III	223 (16%)	67 (17%)	46 (13%)	46 (15%)			
IV	265 (19%)	82 (20%)	58 (16%)	62 (21%)			
Unknown	339 (25%)	87 (21%)	139 (38%)	82 (27%)			

Table 1: Socio-demographic and clinical characteristics of questionnaire respondents, non-respondents and patients with unverifiable addresses.
(Continued)

	Respondents		Non-respondents	Patients with unverifiable addresses	P-value	Respondents vs. non-respondents vs. patients with unverifiable addresses
	N= 1369	Survivors who completed both questionnaires N= 407	N= 364	N= 300		
Primary treatment						
Radiotherapy	368 (27%)	119 (29%)	86 (24%)	79 (26%)	0.13	0.31
Chemotherapy	904 (66%)	280 (69%)	199 (55%)	175 (58%)	0.07	<0.01
Active surveillance	293 (21%)	75 (18%)	111 (31%)	84 (28%)	0.10	<0.01
Stem cell transplantation	69 (5%)	30 (7%)	21 (6%)	11 (4%)	0.01	0.25
Self-reported comorbidity						
No comorbid condition	312 (30%)	114 (30%)			0.41	
1 comorbid condition	329 (31%)	122 (32%)				
2 comorbid conditions	205 (20%)	81 (21%)				
>2 comorbid conditions	202 (19%)	64 (17%)				
Marital status						
Partner	1064 (79%)	337 (84%)			0.01	
No partner	283 (21%)	66 (16%)				
Educational level^s						
Low	243 (18%)	58 (14%)			0.10	
Medium	797 (60%)	247 (61%)				
High	298 (22%)	98 (24%)				
Employment						
Employed	1152 (90%)	386 (100%)			<0.01	
Not working/retired	134 (10%)	-				

I-NHL indolent non-Hodgkin lymphoma; A-NHL aggressive non-Hodgkin lymphoma; HL Hodgkin lymphoma; MM multiple myeloma

^sEducation levels included low = no/primary school; medium = lower general secondary education/vocational training; or high = pre-university education/high vocational training/university

Table 2: Comparison of mean EORTC QLQ-INFO25, EORTC QLQ-C30 and HADS subscale scores between T1 and T2

	Baseline T1 N=1369	Baseline T1 Survivors who completed both questionnaires N= 407	Follow-up T2 (two years later) N= 407	P-value	
	Mean (SD)	Mean (SD)	Mean (SD)	Survivors who completed one vs. two questionnaires	T1 vs. T2‡
EORTC QLQ-INFO25+					
Information about disease	52 (21)	53 (20)	53 (20)	0.95	0.98
Information about medical tests	65 (22)	65 (22)	62 (23)	0.55	<0.01
Information about treatment	47 (23)	48 (22)	45 (23)	0.49	0.01
Information about other services	21 (22)	22 (23)	23 (23)	0.78	0.18
Satisfaction with information	62 (27)	62 (27)	61 (25)	0.99	0.41
Usefulness of information	65 (24)	66 (24)	63 (22)	0.95	0.04
EORTC QLQ-C30++					
Physical functioning	79 (21)	81 (20)	79 (21)	0.02	<0.01
Role functioning	76 (29)	78 (27)	77 (26)	0.12	0.31
Emotional functioning	83 (21)	85 (20)	85 (20)	0.03	0.67
Cognitive functioning	82 (23)	84 (21)	83 (19)	0.07	0.81
Social functioning	84 (24)	86 (23)	87 (21)	0.07	0.16
Quality of life	73 (20)	76 (20)	75 (19)	<0.01	0.71
HADS+++					
Anxiety	4.6 (3.9)	4.0 (3.5)	4.2 (3.7)	<0.01	0.22
Depression	4.3 (3.9)	3.8 (3.5)	3.9 (3.6)	<0.01	0.37

‡ Based on paired t-test

+ Higher score (0-100) indicates more perceived receipt of information;

++ Higher score (0-100) indicates better functioning;

+++ Higher score (0-21) indicates higher levels of anxiety/depression

Survivors' HRQoL scores and anxiety and depression levels did not change across the two time points, except for physical functioning which slightly but significantly decreased (81 vs. 79, $p < 0.01$; Table 2). This decrease was not clinically meaningful²⁴. Survivors <2 years since diagnosis showed no differences in functioning, anxiety and depression levels over time.

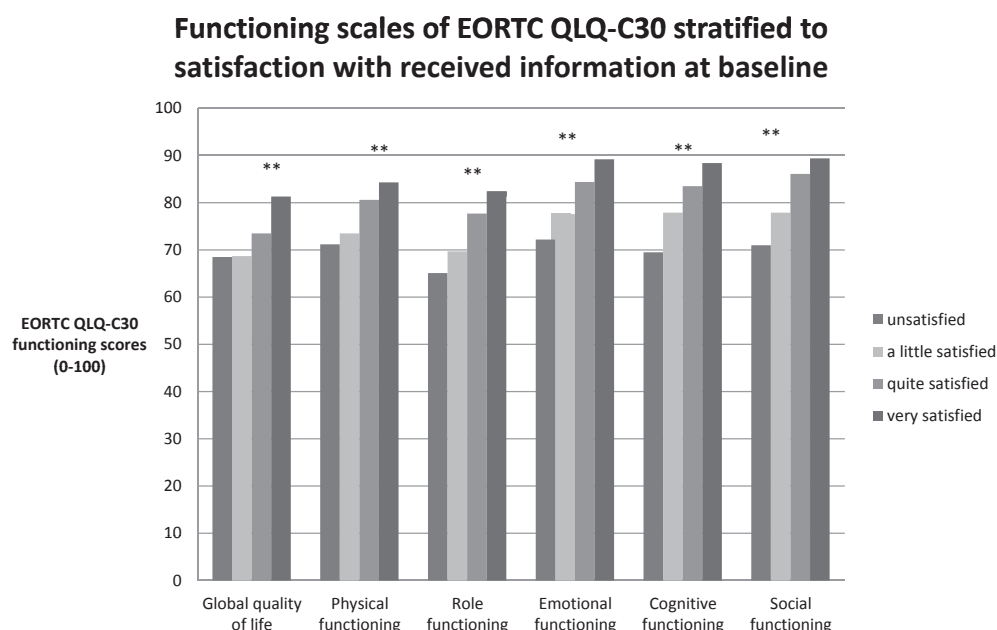
Associations of information provision with HRQoL, anxiety and depression at baseline (T1)

Survivors who were satisfied with the received information reported better HRQoL (Figure 2) and lower levels of anxiety and depression compared to unsatisfied survivors.

Multivariate linear regression analyses showed that, at baseline, receiving more *disease-*

related information was associated with lower levels of anxiety ($\beta=-0.10$) and depression ($\beta=-0.10$; $p<0.05$), while receiving more information about the *treatment* was associated with worse emotional ($\beta=-0.10$) and cognitive functioning ($\beta=-0.11$) and higher levels of anxiety ($\beta=0.12$) and depression ($\beta=0.09$; all $p<0.05$). The perceived receipt of more information about *other services* was related to worse functioning on all scales (β ranging from -0.09 to -0.14), except for emotional functioning, and higher levels of anxiety ($\beta=0.10$) and depression ($\beta=0.07$). Higher *satisfaction* with the received information was associated with better HRQoL (β ranging from 0.13 to 0.22) and lower levels of anxiety ($\beta=-0.23$) and depression ($\beta=-0.21$; all $p<0.01$).

Figure 2: HRQoL according to the level of satisfaction with the received information at T1.



** $p<0.01$

Associations of information provision on T1 with HRQoL, anxiety and depression on T2

Multivariate linear regression analyses including the covariates age, sex, time since diagnosis, tumour type, disease stage, number of comorbidities, educational level and marital status showed that receiving more information about the *treatment* at baseline (T1) was associated with worse emotional functioning ($\beta=-0.18$, $p<0.05$) at T2, and more information about *other services* at T1 was associated with worse social functioning ($\beta=-0.15$, $p<0.05$) at T2. Higher *satisfaction* with the received information at T1 was associated

with better HRQoL (β ranging from 0.15 – 0.25; all $p < 0.05$) on all scales at T2, except for cognitive functioning.

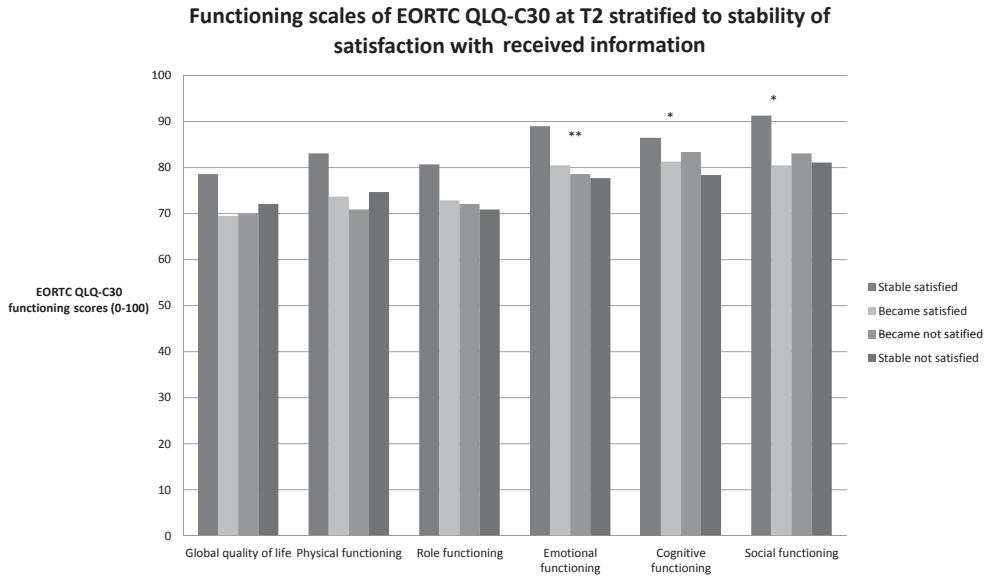
After correction for baseline HRQoL, the relationship of satisfaction with the received information remained only significant for role functioning ($\beta = 0.17$, $p < 0.05$) and global quality of life ($\beta = 0.14$, $p < 0.05$). Subanalyses for survivors < 2 years since diagnosis showed the same relationships.

Stable satisfied survivors (56%) reported better HRQoL and lower levels of anxiety and depression at T2 compared to survivors who were unsatisfied (13%) or with changing satisfaction levels over time (30%; Figure 3). Multivariate linear regression analyses corrected for baseline HRQoL and covariates showed that the stability of satisfaction with received information predicted emotional, cognitive and social functioning (β ranging from -0.09- -0.13, $p < 0.05$).

DISCUSSION

This population-based study among lymphoma and MM survivors showed that survivors with high levels of satisfaction with received information had the highest HRQoL and lowest anxiety and depressive symptom levels. The perceived receipt of information decreased slightly over time (mostly among short-term survivors), while HRQoL, anxiety and depression levels did not change over time. The receipt of more *disease-related* information was associated with lower levels of anxiety and depression, while the receipt of more information about the *treatment* and *other services* was associated with worse HRQoL and higher levels of anxiety and depression. Satisfaction with the received information at baseline was associated with HRQoL 2-years later, however after correction for baseline HRQoL the relationships partly disappeared. Satisfaction with the received information at both time points was associated with better emotional, cognitive and social HRQoL compared to fluctuating satisfaction levels or constant dissatisfaction with the received information.

The perceived levels of information about *treatment* and especially about other services were low at both assessment periods. The negative associations of information about *treatment* and *other services* with HRQoL, anxiety and depression could therefore indicate that this information was not enough, possibly leading to more uncertainty or confusion. This is confirmed by our finding that the most frequently mentioned topics survivors wanted more information about were possible side- and long-term effects of their treatment, late effects of cancer on different aspects of life and aftercare. However, patients with a higher stage disease might indicate to receive more information, but still have worse HRQoL and higher levels of anxiety and depressive symptoms as a consequence of their disease severity.

Figure 3: HRQoL at T2 according to the stability of satisfaction with the received information over time.

* $p < 0.05$; ** $p < 0.01$;

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Satisfaction with received information was associated with better HRQoL and lower levels of anxiety and depression. Although levels of received information (quantity) determine part of the satisfaction levels of cancer survivors, the quality of information (the degree to which information needs are met) is even more important. For some survivors the topics they wanted more information about were constant over time, possibly indicating that these needs remained unmet. Other survivors reported changing needs over time. HCPs must be aware of the possible (changing) needs of cancer patients, however studies show that there is a discrepancy between the actual information needs of the patient and the perception of HCP about the needs of the patients ²⁵.

The relationship between satisfaction with received information and HRQoL, anxiety and depression largely disappeared after correction for baseline levels. A limitation of these analyses is that they focus on mean differences and not on individual changes. Given the large standard deviations of the information provision scales, there is a high degree of variation between individuals. Therefore we decided to make a distinction between survivors who remained stable satisfied or dissatisfied or patients who had fluctuating satisfaction levels. Our results show that stable satisfied survivors had the highest levels of mental HRQoL also after adjusting for baseline levels. These positive mental health outcomes can be the direct result of conversations between HCP and patient from which patients feel recognized,

validated, trusted, worthy, reassured and comforted^{26, 27} and indirectly through diagnosis and treatment of mental problems (anxiety and depression) and strengthened social support. Alternatively, it is possible that patients with higher levels of HRQoL and lower levels of distress naturally report higher levels of satisfaction with the received information, independent of the information they actually received.

Our results suggest that it is important to satisfy the patient and to keep the patient satisfied with respect to information. The best way to unravel the information needs of a patient is to consult the patient him or herself, however this is rarely done²⁸. Furthermore, HCPs often do not check the understanding of the patient²⁹. Recently, some strategies were devised to address the information needs of cancer survivors. First, survivorship care plans provide cancer survivors with a summary of their treatment as a formal document that also includes recommendations for subsequent cancer surveillance, management of late effects, and strategies for health promotion³⁰⁻²⁹. Second, feedback of patient reported outcomes (PRO) to the HCP has the potential to help detect unmet needs and symptoms, leading to better control and monitoring of such issues, serve as a guide for HCP to discuss HRQoL issues, act as patients' voice, and facilitate individualized information provision and care³¹⁻³². Last, a recent founded Working Group of haematologists, radiation oncologists, epidemiologists and internists aimed to establish survivorship clinics with the goal to improve survivors' HRQoL by informing survivors about long-term risks, advice preventive measures, suggest screening and improve aftercare by providing rehabilitation programs³³. Participation of survivors could be an efficient solution to address the unmet information needs.

The present study has limitations that should be mentioned. First, although the response rate at baseline was high and information was present concerning socio-demographic and clinical characteristics of the non-respondents and patients with unverifiable addresses, whether non-respondents declined to participate in the study because of poor health remains unknown. Secondly, a large part of the survivors did not respond to the second questionnaire, these non-responders had worse HRQoL scores at T1, which possibly caused some selection bias at T2. Third, the mean time since diagnosis was almost 4 years, which could influence the recall effect of information received. However we did not found differences in the perceived receipt of information among short- and long-term survivors and the majority of patients was still under active follow-up. Fourth, the EORTC QLQ-INFO25 only measures the information patients indicated to have received, it is not clear how much information was actually provided. It would therefore be interesting to compare data on actual information provision with data from questionnaires. Patient information delivery and perception are part of a complex process that is influenced by many factors including preexisting patient-related psychological and behavioral patterns, which can influence our

results. Finally, since the EORTC QLQ-INFO25 is not a measure of clinical outcomes it was not possible to determine clinically meaningful differences. The declines in perceived receipt of information over time were statistical significant but small, while HRQoL, anxiety and depression did not change over time. It is therefore difficult to determine causal associations. An intervention study which aims to improve information provision could provide more insight into the causality of these relations.

Despite the limitations noted, the present study showed that satisfaction with the received information among lymphoma and MM survivors was associated with better HRQoL and lower levels of anxiety and depression. Survivors who were satisfied with the received information on both time points report better mental HRQoL. HCPs should provide patients with information adapted to patients needs in order to satisfy survivors and also to keep them satisfied. The effectiveness of PRO feedback, survivorship care plans and the foundation of survivorship clinics on patient satisfaction with information should be investigated in future studies.

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CHAPTER 8

Rising incidence, no change in survival and decreasing mortality from thyroid cancer in The Netherlands since 1989

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ABSTRACT

Background: The incidence of thyroid cancer (TC) is increasing worldwide, partly due to increased detection. We therefore assessed combined trends in incidence, survival and mortality of the various types of TC in The Netherlands between 1989 and 2009.

Methods: We included all patients ≥ 15 years with TC, diagnosed in the period 1989–2009 and recorded in The Netherlands Cancer Registry (N = 8021). Information on age, gender, date of diagnosis, histological type of tumour and TNM classification was recorded. Mortality data (up to 1 January 2010) were derived from Statistics Netherlands. Annual percentages of change in incidence, mortality, and relative survival were calculated.

Results: Since 1989 the incidence of TC increased significantly in The Netherlands (estimated annual percentage change (EAPC) = +1.7%). The incidence rates increased for all age groups (except for females ≥ 65 years), papillary tumours (EAPC = +3.6%), T1 and T3 tumours (EAPC = +7.9% and +5.8% respectively). Incidence rates decreased for anaplastic (EAPC = -1.9%) and T2 and T4 tumours (EAPC = -1.1% and -2.3% respectively). Five-year relative survival rates remained stable, however appeared to be somewhat higher for papillary (93%) and follicular (87%) TC, all age groups and T1-T3 tumours (95%, 94% and 80% respectively) and somewhat lower for T4 (52%) and medullary tumours (68%) in the 2004-2009 period compared to earlier periods. Mortality due to TC decreased (EAPC = -1.9%).

Conclusion: TC detection and incidence has been rising in The Netherlands, while mortality rates are decreasing and survival rates remained stable.

INTRODUCTION

In recent years, the incidence of thyroid cancer (TC) has increased drastically in the US and most European countries ^{1,2}. TC is the most common endocrine malignancy ³. The higher incidence rates are often attributed to increased environmental radiation exposure ⁴, radiation therapy for the treatment of the head and neck areas ⁵, lower iodine nutrition ⁶ or higher prevalence of obesity ⁷. The exact etiology of TC remains unclear. It is also suggested that increasing use of more precise diagnostics, like cervical ultrasound and fine needle aspiration biopsy (FNAB), contribute to an increased identification of subclinical disease ^{2,8}. Although a larger portion of small tumours then appears to have been detected, slightly increased incidence rates of larger tumours are also observed ⁸. Contrary to the increasing incidence, mortality from TC remained stable in north America ² and decreased (–23% and –28%, for men and women respectively) in the European Union ⁹ and prognosis is good (except for the anaplastic type of tumour).

The combined measurements of TC burden (i.e., incidence, mortality and survival) could indicate whether and where progress had been made in cancer diagnosis and treatment and where improvements might be needed. As none of the previous studies described all three determinants of TC burden in combination, we assessed long-term trends in incidence, mortality, and survival of TC in The Netherlands between 1989 and 2009. We hypothesized that in the absence of a clear pattern of etiological/environmental exposures the rising incidence might be largely due to increased diagnostic scrutiny, leading to an increased detection of small tumours. If the incidence of small tumours would increase, due to its excellent prognosis, we expect the overall mortality rate to decrease and survival rates to increase.

MATERIALS AND METHODS

Data collection

Population-based data were used from the nation-wide Netherlands Cancer Registry (NCR), which was started in 1989 and combines data from eight Dutch regional cancer registries, currently merged into two. The NCR is based on notification of all new diagnosed malignancies in The Netherlands by the automated pathological archive (PALGA), supplemented by notifications from the national registry of hospital discharge, various clinical chemistry laboratories and radiotherapy institutions. Information on patient (sex, date of birth) and tumour characteristics (date of diagnosis, histology, location, stage (TNM (Tumour-node-metastasis) classification ¹⁰⁻¹²)) were routinely obtained from the medical records 6-12 months after diagnosis.

Vital status was actively obtained on a regular basis from the municipal registries and from the database of deceased persons of the Central Bureau for Genealogy (date of last follow-up: 1st January 2010). Survival time was calculated as the time from diagnosis to death or to 1st January 2010 or to date of emigration.

Topography and histology were coded according to the International Classification of Diseases for Oncology (ICD-O-3) ¹³. All tumours with an ICD-O-3 topography code thyroid (C73) diagnosed in the period 1989-2009 were included in this study (n= 8021). The following histological categories were used: papillary cancer (morphology codes 8050, 8201, 8260, 8340-8344, 8350, 8504; and differentiation grade = 1 or 2), follicular cancer (8290, 8330-8332, 8335; and differentiation grade = 1 or 2), poorly differentiated TC (8010, 8012; and differentiation grade = 3; or 8050, 8140, 8201, 8260, 8290, 8330-8332, 8335, 8340-8344, 8350, 8337, 8504; and differentiation grade = 3 or 4; 8337), medullary cancer (8345, 8510-8512), anaplastic cancer (8010, 8012; and differentiation grade = 4; or 8020-8035, 8041, 8575, 8980) and other. T stage was based on pathological T stage. For cases where pathological stage was unknown, clinical stage was used.

Patients <15 years and >95 years were excluded from the survival analysis, as well as cases diagnosed at autopsy. Age at diagnosis was divided into four groups (<45; 45-59; 60-74; ≥75 years). The study period was divided into four categories of 5 years and one of 6 years: 1989-1993, 1994-1998, 1999-2003, and 2004-2009. Incidence rates were calculated per age group, sex, histological type and T stage.

Statistical analyses

Annual incidence and mortality rates for the period 1989-2009 were calculated per 100,000 person-years, using the mid-year population size as obtained from Statistics Netherlands. Rates were age-standardized to the European standard population (European Standardized Rates (ESR)). Trends in incidence were evaluated by calculating the estimated annual percentage change (EAPC) and the corresponding 95% confidence intervals (95% CI). To calculate this, a regression line was fitted to the natural logarithm of the rates, using the calendar year as regressor variable (i.e. $y = ax + b$ where $y = \ln(\text{rate})$ and $x = \text{calendar year}$, then $\text{EAPC} = 100 * (e^a - 1)$). This calculation assumes that the rates increased or decreased at a constant rate over the entire period. Joinpoint analyses were performed to discern significant changes in the trend and, if present, when they occurred ¹⁴.

Relative survival was used as an estimation of disease-specific survival. It was derived as the ratio of observed survival of the cancer patients and the expected survival of a comparable age- and sex-matched group of the general population while using the Ederer method ¹⁵. Traditional, cohort-based, relative survival analysis was used to calculate 5-year relative survival. For the 5-year relative survival estimates of the last period (2004-2009) only the patients diagnosed in 2004 had 5-year follow-up. Recent changes in survival might therefore

not be accurately represented by standard cohort 5-year survival estimates. Period-based relative survival analysis should provide the most-up-to-date estimates for recent time periods.

Survival trends were quantified as the mean period percentage change (MPPC) within the period 1989-2009 estimated by a linear regression model. A positive value of the mean period change implies an upward trend in survival (i.e. improving) and a negative value implies a negative trend (i.e. deterioration).

Multivariate relative survival analyses, using Poisson regression modeling, were carried out to estimate relative excess risk (RER) of dying adjusted for follow-up interval and age group. SAS software (SAS system 9.2, SAS Institute, Cary, NC) was used to perform the statistical analyses.

RESULTS

Trends in incidence

In The Netherlands 8021 new TC cases were registered between 1989 and 2009. Mean age at diagnosis was 53 ± 19 (standard deviation (SD)) years. The female to male ratio was 2.4:1. The proportion male patients <45 years decreased steadily from 38% in 1989-1993 to 32% in 2004-2009. In females, 40% were < 45 years of age at diagnosis. Furthermore, the proportion patients 45-59 years increased (Table 1).

The overall incidence rate increased from 2.0 in 1989 to 2.9 per 100,000 person years in 2009 (EAPC= +1.7%; 95% CI: 1.2-2.3), corresponding to an increase from 315 cases in 1989 to 537 in 2009. For females the incidence rate increased from 3.1 in 1989 to 4.1 per 100,000 person years in 2009 (EAPC= +1.7%; 95% CI: 1.1-2.4). The EAPC for females changed from +0.1% (95% CI: -0.9-1.2) before 2001 to +4.7% (95% CI: 2.7-6.7) after 2001. For males the incidence rate increased from 1.0 in 1989 to 1.7 per 100,000 person years in 2009 (EAPC= +1.6%; 95% CI: 1.2-2.3). Incidence rates increased for all age groups, except for females ≥ 65 years (Figure 1a).

The percentage of papillary TC cases increased for males from 47% in 1989 to 61% in 2009 and for females from 51% in 1989 to 67% in 2009 ($p < 0.01$; Table 1). The overall incidence rate increased for papillary TC from 1.0 in 1989 to 2.1 per 100,000 person years in 2009 (EAPC = +3.6%; 95% CI: 3.0-4.2). The EAPC for papillary TC changed from +0.7% (95% CI: -1.9-3.3) before 1996 to +4.9% (95% CI: 3.8-5.9) after 1996, this trend was only found for females (Figure 1b). The incidence of follicular and medullary TC remained relatively stable and the incidence of anaplastic TC decreased slightly over time (EAPC = -1.9%; 95% CI: -3.3 - -0.5) for both sexes.

Table 1: Age, histology, and T stage of thyroid cancer patients in The Netherlands, 1989-2009 (n=8021) according to period and sex

	Males				Females			
	1989-1993 N=437 %	1994-1998 N=504 %	1999-2003 N=542 %	2004-2009# N=858 %	1989-1993 N=1149 %	1994-1998 N=1188 %	1999-2003 N=1335 %	2004-2009# N=2008 %
Age(years)								
<45	38	34	33	32	40	40	43	39
45-59	28	26	29	29	19	23	23	26
60-74	23	25	23	26	26	22	18	19
≥75	12	15	15	13	15	15	15	16
Histology								
Papillary carcinoma	47	49	55	61	51	56	62	67
Follicular carcinoma	22	20	20	19	25	22	19	16
Poorly differentiated carcinoma	6	7	4	4	5	4	5	4
Medullary carcinoma	14	14	11	10	7	8	5	5
Anaplastic carcinoma	8	8	8	4	9	8	7	6
Other	3	2	3	2	3	3	2	3
T stage								
1	12	16	16	29	14	15	19	36
2	35	29	31	20	40	43	41	25
3	13	14	16	27	11	12	12	20
4	22	21	20	14	21	18	18	12
X	18	20	16	10	14	12	10	7

6-year period

For T1 disease, the incidence rate increased from 0.2 in 1989 to 1.1 per 100,000 person years in 2009 (EAPC= +7.9%; 95% CI: 5.8-10.0) and for T3 disease the incidence rate increased from 0.2 in 1989 to 0.7 per 100,000 person years in 2009 (EAPC= +5.8%; 95% CI: 4.1-7.6). The EAPC for T1 changed from +2.1% (95% CI: -1.3-5.6) before 2002 to +14.3% (95% CI: 3.5-26.3) after 2002 and T3 changed from +0.2% (95% CI: -2.6-3.1) before 2002 to +9.5% (95% CI: 5.9-13.1) after 2002, these jointpoints were only found for females (Figure 1c). The overall incidence rate of T2 disease remained stable from 0.8 in 1989 to 0.7 per 100,000 person years in 2009 (EAPC= -1.1%; 95% CI: -2.2 - - 0.02). For females, the EAPC for T2 changed from +1.6% (95% CI: 0.2-3.0) before 2002 to +3.9% (95% CI: 3.5-26.3) after 2003 (with and decrease of -49.6% between 2002 and 2003 due to the change in TNM classification; Figure 1c). This trend was not found for males (EAPC= -1.3% (95% CI:-3.4-0.9)). The incidence rate for T4 disease decreased by -2.3% (95% CI: -3.3 - -1.4) per year between 1989-2009; and changed from -0.2% (95% CI: -2.4-2.0) before 2002 to -2.4% (95% CI: -5.6-1.0) after 2002.

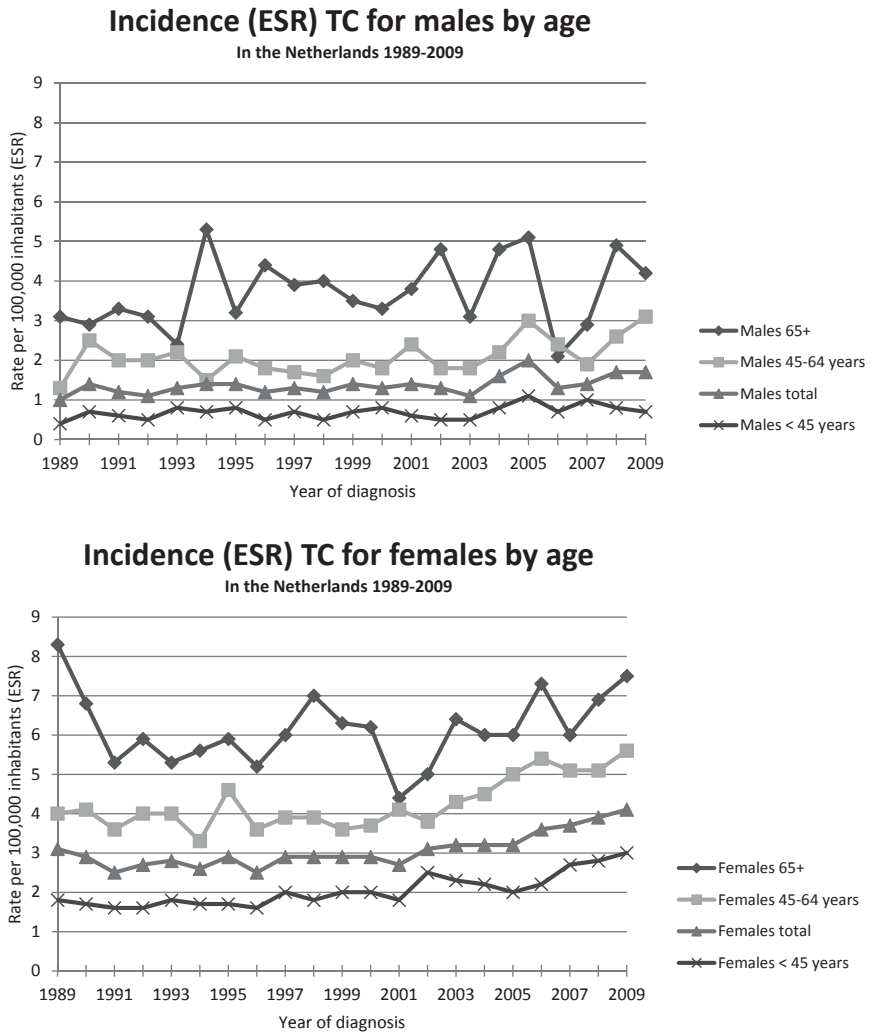


Figure 1a: Three-year moving average of age-standardized incidence rates (ESR) of thyroid cancer in The Netherlands 1989-2009 according to gender and age group at diagnosis.

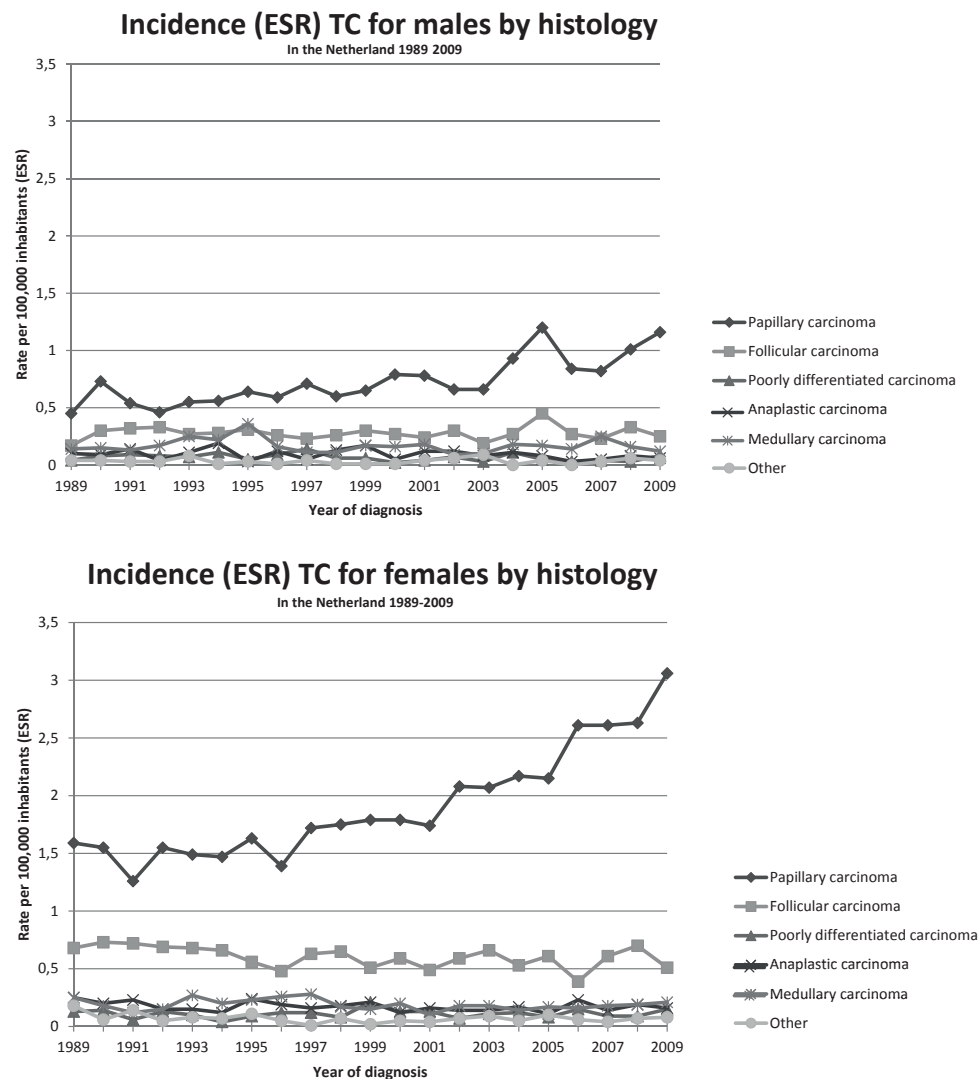


Figure 1b: Three-year moving average of age-standardized incidence rates (ESR) of thyroid cancer in The Netherlands 1989-2009 according to gender and histology.

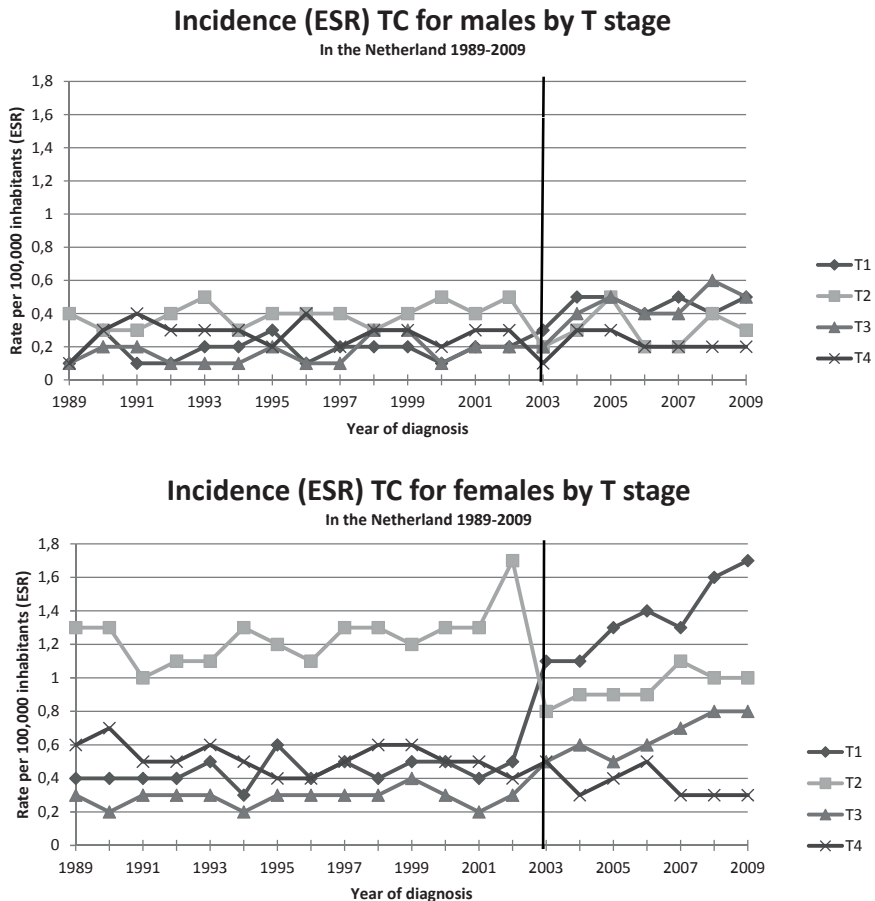


Figure 1c: Three-year moving average of age-standardized incidence rates (ESR) of thyroid cancer in The Netherlands 1989-2009 according to gender and T stage.

Vertical line represents the change in TNM classification in 2003. UICC 5th edition: T1 tumour size maximal 1 cm; T2 tumour size > 1 cm and ≤ 4 cm; T3 tumour size > 4 cm limited to the thyroid; T4 any tumour with extrathyroid extension ¹¹. UICC 6th edition: T1 tumour size maximal 2 cm; T2 T2 tumour size > 2 cm and ≤ 4 cm; T3 tumour size > 4 cm limited to thyroid or minimal extrathyroid extension; T4 tumour extends beyond thyroid capsule ¹²

Relative survival

Overall, five-year relative survival from TC remained stable, although appeared to increase in males from 74% in 1989-1993 to 82% in 2004-2009 and in females from 78% to 81% (Table 2). While in 1989-2003, 5-year relative survival was better for females than in males, this discrepancy disappeared after 2003. Five-year relative survival decreased with increasing age at diagnosis, being ~98% for <45 years, ~88% for 45-59 years, ~61% for 60-74 years and ~42% for 75+ years in the entire study period, and increased non-significantly for all age

groups over time. Survival decreased with increasing stage of disease, with 5-year relative survival of ~95% for T1 disease in the entire period 1989-2009, while the 5-year relative survival for T2, T3, T4 disease were respectively, ~94%, ~80%, and ~52% in the entire study period. A non-significant increase over time was seen in survival of T1, T2, T3 thyroid cancer, while survival from T4 appeared to decrease over time. Five-year survival rates remained more or less stable for papillary TC (~93%) and follicular TC (~87%) over the entire study period and appeared to decrease slightly for medullary TC from 68% to 64% in 2004-2009. The 1-year relative survival for anaplastic thyroid cancer decreased from 16.2% in 1989-1993 to 14.5% in 2004-2009.

Table 2: Five-year relative survival (standard error) by period of diagnosis, T stage, and age

	1989-1993	1994-1998	1999-2003	2004-2009 ^a	Period change (95%CI)	P value
Sex						
Male	74 (2.5)	74 (2.4)	74 (2.3)	82 (2.1)	2.5 (-3.2-8.2)	0.20
Female	78 (1.4)	81 (1.3)	83 (1.2)	81 (1.4)	1.1 (-1.7-3.9)	0.23
Age (years)						
<45	97 (0.8)	97 (0.7)	98 (0.5)	98 (0.7)	0.5 (-0.3-1.4)	0.11
45-60	86 (2.1)	86 (1.8)	89 (1.6)	90 (1.6)	1.5 (-0.2-3.2)	0.06
60-75	59 (2.8)	58 (2.9)	59 (2.9)	67 (3.1)	2.5 (-4.4-9.4)	0.26
75+	36 (4.4)	48 (4.8)	40 (4.2)	42 (4.9)	1.1 (-11-13)	0.78
T stage						
1	94 (2.2)	95 (1.8)	95 (1.5)	97 (1.0)	1.0 (-0.6-2.6)	0.12
2	92 (1.5)	95 (1.2)	94 (1.1)	94 (1.8)	0.6 (-2.4-3.5)	0.51
3	76 (4.2)	79 (3.6)	84 (3.0)	80 (3.1)	2.0 (-3.5-7.4)	0.26
4	59 (3.2)	56 (3.2)	56 (3.0)	39 (3.7)	-5.8 (-17-5.7)	0.16
X ^b	45 (4.2)	43 (3.9)	37 (4.0)	37 (5.5)	-2.9 (-6.4-0.6)	0.07
Histology						
Papillary carcinoma	93 (1.2)	93 (1.1)	94 (1.0)	93 (1.1)	0.2 (-1.0-1.3)	0.61
Follicular carcinoma	87 (2.2)	88 (2.4)	88 (2.2)	86 (3.2)	-0.3 (-2.6-2.0)	0.63
Poorly differentiated carcinoma	27 (5.3)	20 (5.1)	35 (5.7)	44 (7.7)	6.6 (-6.5-20)	0.16
Anaplastic carcinoma	0	0	0	0	0	n.a.
Medullary carcinoma	68 (4.5)	78 (3.8)	62 (4.9)	64 (5.8)	-2.8 (-17-11)	0.46
Other	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.

^a based on period analyses

^b primary tumour cannot be assessed

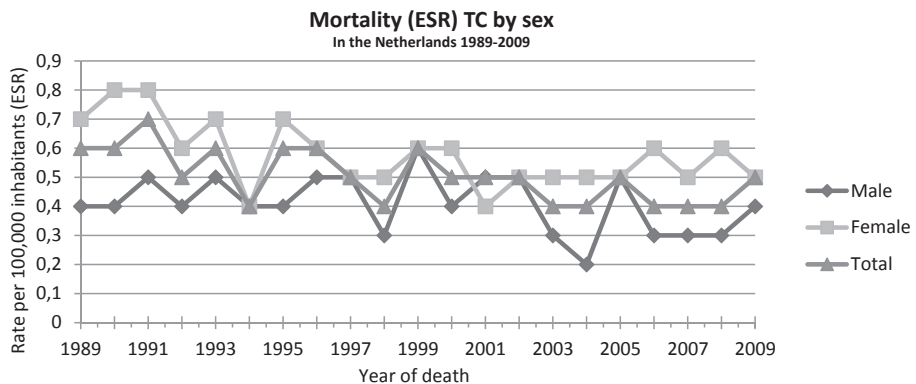
n.a. not available

Multivariable relative survival analyses showed an increased risk of death for older patients, patients with a higher stage disease and a poorly differentiated, anaplastic or medullary tumour type, however no effect for period was found (Table 3).

Table 3: Relative excess risk (RER) of dying for thyroid cancer patients in The Netherlands

Variable	RER	95% CI
Period of diagnosis		
1989-1993	1	
1994-1998	1.0	0.9-1.2
1999-2003	1.2	1.0-1.4
2004-2008	1.0	0.8-1.2
Sex		
Male	1	
Female	0.9	0.8-1.1
Age group (years)		
<45	1	
45-59	3.2*	2.4-4.4
60-75	7.2*	5.4-9.6
75+	9.9*	7.4-13.4
Stage of the disease		
1	1	
2	1.5	1.0-2.2
3	2.4*	1.6-3.5
4	4.2*	2.9-6.2
X ^a	8.0*	5.5-11.8
Histology		
Papillary carcinoma	1	
Follicular carcinoma	1.0	0.8-1.3
Poorly differentiated carcinoma	6.5*	5.2-8.1
Anaplastic carcinoma	16.9*	13.9-20.7
Medullary carcinoma	3.9*	3.0-4.9
Other	5.9*	4.4-7.9

* P<0.05; Adjusted for follow-up interval

^a primary tumour cannot be assessed**Figure 2:** Three-year moving average of age-standardized mortality rates of thyroid cancer in The Netherlands 1989-2009 according to gender and age group at diagnosis

Trends in mortality

Mortality decreased with -1.9% (95% CI:-2.8- -0.9) per year between 1989 and 2009 (Figure 2), more in males (-2.2%) than in females (-1.7%). In absolute numbers we observed a slight increase from 98 deaths in 1989 to 105 deaths in 2009.

DISCUSSION

Our study shows that since 1989 the incidence of TC increased significantly in The Netherlands, while mortality from TC decreased. This increase was due to papillary tumours only. Five-year relative survival remained stable and appeared to be somewhat higher for both sexes, all age groups and T1-T3 tumours and somewhat lower for T4 and medullary tumours in the period 2004-2009 compared to earlier periods. The one-year survival rate of anaplastic tumours remained low.

The rising age-standardized incidence of TC in The Netherlands is in concordance with patterns observed in many other European countries and the US ¹. The increase in our study was mainly due to the increased number of detected early stage tumours (T1) of papillary histological subtype. This shift to the detection of more early stage papillary tumours can partly be explained by the change in TNM classification in 2002, however the T1 incidence rates were already increasing before 2002 ¹⁶ and incidence rates for T2 were also increasing after 2002. The incidence rates started to increase at a younger age in women than in men, possibly related to greater use of health care services by young and middle-aged women compared to men of the same age ¹⁷. Also, the incidence rate of papillary TC increased more steeply among women than men, likely because of the higher number of biopsies performed in this population ¹⁸.

The main question debated in the literature is whether or not the observed increase in TC incidence is the result of a real increase in number of cases or of improved detection? A recent study in the US showed a significant decrease in tumour size over time and concluded that the apparent increase in TC incidence was largely due to more detection of subclinical disease ⁸. It has been shown that TC can exist as subclinical entity since at least one third of the adults have subclinical TC at autopsies ¹⁹. Improved detection by the increased use of and improved (resolution of) diagnostic tools and medical surveillance might be responsible for the detection of more subclinical disease and could also have resulted in a shift in detection from more advanced tumours to early stage tumours ¹⁸. Nevertheless, incidence rates also increased for T3 tumours, and this increase was larger than the decrease in incidence rates of T4 tumours. This increasing trend might be less related to the improved detection and increased surveillance. True increases in incidences of TC have been

associated with different risk factors like exposure to ionizing radiation (fallout, diagnostic tests like computed tomography scans and treatments like radiotherapy), low iodine intake^{6 20} and overweight⁷. However, none of these factors have been proven as risk factors in The Netherlands. Therefore more research into the events involved in the initiation and progression of thyroid cancer is needed.

Five-year relative survival rates for differentiated TC were high and within the range of rates described for the US²¹ and Europe²². The small differences suggest corresponding differences in the availability of diagnostic and treatment options, and in the effectiveness of healthcare systems. The non-significant decrease in five-year relative survival rates for T4 tumours could be explained by the decrease in incidence of the slowly growing T4 tumours, indicating that those tumours are earlier detected as T3 tumours. Furthermore, since 2002 any tumour with minimal extrathyroidal extension is registered as T3 instead of T4 and anaplastic tumours are also registered as T4, leaving the truly advanced cancers with a worse prognosis as T4, which could explain the decrease in survival rates for these tumours. Five-year relative survival rates for anaplastic (5.6 – 11.4% depending on race) and medullary cancer (73.5 – 88.7% depending on race) were higher in the US compared to The Netherlands²¹. The low incidence rates of both tumours have limited the development of clinical expertise and conduction of randomized clinical trials²³. The American Thyroid Association recently came up with evidence-based management guidelines for medullary²³ and anaplastic TC²⁴. Dissemination of standardized guidelines to Europe is important to ensure optimal treatment for these patients. Recently, a study showed improved disease-specific survival for a subpopulation of anaplastic TC patients who were treated by aggressive multimodal regimes based on a prognostic index²⁵. Application of this prognostic index in The Netherlands could possibly lead to some improvements in survival rates for this most lethal tumour.

The increased incidence of TC was not accompanied by a concurrent increase in TC mortality which even decreased for both men and women, equal to other studies in Europe⁹ and the US²⁶. Many of the detected tumours were indeed small treatable cancers. The detection of these small tumours could have preceded development of more advanced cancers (T4) or tumours with more unfavourable prognosis such as medullary and anaplastic cancers whose incidence decreased and whose prognosis remained stable or decreased.

Since a large part of the increased incidence in our study can be ascribed to the detection of small (subclinical) tumours, overdiagnosis of clinically irrelevant cancer might be occurring²⁷. Indeed, most patients with cytological indeterminate nodules are referred for diagnostic thyroid surgery, but the majority (66%) prove to have benign disease²⁸

and for these patients surgery is unnecessary ²⁹. It has been hypothesized that increased detection of low risk tumours can lead to an overestimation of treatment efficacy and a subsequent rise in use of treatment ³⁰. Up to now, there is a lack of randomized controlled trials to support management decisions for small and low-risk tumours. For patients with early-stage differentiated TC whose primary tumour is > 1 cm the guidelines recommend total thyroidectomy and radioactive iodine treatment to be selectively considered ⁹. Nevertheless, treatment with radioactive iodine is of uncertain benefit for patients with low-risk disease ³¹. In addition, the majority of patients with early-stage differentiated TC will have a favorable outcome and many of these tumours would remain asymptomatic during lifetime ³². However a small proportion of these patients will experience recurrent disease with increased morbidity ³³. There is a need to improve the preoperative evaluation of low-risk thyroid nodules in order to prevent potential overtreatment and in addition to this a more conservative surgical approach without radioiodine therapy should be considered for low risk patients ³³. A complete understanding of the various prognostic factors is important to advise the patient accordingly on the best treatment and long-term surveillance ²⁶. This is important since we recently showed that problems and symptoms of TC and its treatment can be detected up to 20 years after diagnosis ³⁴. These late symptoms were mostly related to thyroid dysregulation (neuromuscular, concentration, sympathetic, psychological and sensory problems) and not so much to specific morbidities as a consequence of surgery (voice problems, throat/mouth problems and problems with scar). Long term health problems are becoming more important since the prevalence of TC survivors who received more or less aggressive/invasive treatment is increasing and will probably lead to an increased burden on health care in the coming years.

By combining the three epidemiologic determinants of TC burden (i.e., incidence, mortality and survival) with essential prognostic determinants we achieved a more comprehensive assessment of the progress against TC, however also quality of life assessments should be added ³⁵. Some limitations of this study require consideration. Despite the rather clinical nature of the Netherlands Cancer Registry (NCR), lack of details regarding applied primary treatments in our population-based registry limited the potential to explore and elucidate specific reasons for the observed changes in survival. Also, information on the exact tumour size is lacking in the NCR. Thirdly, to calculate 5-year relative survival, we used two different methods, i.e., cohort- and period-based survival analyses. However, the cohort- and period-based 5-year relative survival estimates exhibited relatively small differences.

In conclusion, TC detection and incidence has been rising in The Netherlands, while mortality rates are decreasing and survival rates remained stable and appeared to be somewhat higher except for advanced tumours of which the frequency decreased markedly.

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CHAPTER 9

Health-related quality of life among thyroid cancer survivors: a systematic review

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ABSTRACT

Background: Treatment and follow-up care procedures of thyroid cancer impose great challenges on survivors and could potentially affect their health-related quality of life (HRQoL).

Methods: Two authors systematically reviewed the available literature on HRQoL of thyroid cancer survivors. A PubMed literature search for original articles published until February 2011 was performed. Twenty-seven articles, conducted between 1997 and 2010, which met the predefined inclusion criteria, were subjected to a quality checklist.

Results: All selected studies, except one, were of adequate or good quality. Surgery had a negative impact on short-term HRQoL scores, but these scores returned to preoperational levels when time since surgery increased. Long-term thyroid hormone therapy (levothyroxine) can lead to abnormalities like hyperthyroidism. HRQoL was most affected during thyroid hormone withdrawal for radioiodine remnant ablation or follow-up procedures. The use of recombinant human thyroid stimulating hormone instead of hormone withdrawal leads to considerable improvements in HRQoL during follow-up testing. The results for (long-term) survivors were contradicting. While most (long-term) survivors report some specific long-lasting health problems, some studies found a lower HRQoL for thyroid cancer survivors compared with a healthy population or other reference groups, whereas other studies found similar HRQoL levels.

Conclusion: This review indicates that thyroid cancer survivors generally have a similar or slightly worse HRQoL compared to the normative population, however they report some specific medical problems after cancer treatment and follow-up tests which have a direct negative impact on their current HRQoL and could affect their long-term HRQoL. Specific longitudinal survivorship studies are lacking.

INTRODUCTION

The incidence of thyroid cancer is rising worldwide. As the mortality rate remains relatively stable, the number of thyroid cancer survivors is growing, with over 430,000 people with a history of thyroid cancer in the United States in 2007 ^{1,2}. Treatment of thyroid cancer mostly involves surgery (total thyroidectomy or hemithyroidectomy with or without lymphadenectomy) followed by radioiodine ablation therapy. These aggressive surgical and postoperative treatments are associated with toxicity and long-term physical and psychological morbidity ³. The removal of the total thyroid gland is accompanied by a lifelong dependence on exogenous thyroid hormone (levothyroxine). Despite the efficacy of these primary treatments and the high long-term survival rates, the disease can recur even decades later. Therefore long-term follow-up (neck ultrasonography; serum thyroglobulin (Tg) measurement following TSH stimulation; iodine-131 whole body scanning (WBS)), is necessary and associated with physical and psychological discomfort. In case of recurrence, additional radioiodine treatment or surgery is indicated. The treatment and follow-up care procedures impose great challenges on thyroid cancer survivors and could potentially affect their health-related quality of life (HRQoL).

The aim of cancer treatment is not only to increase survival but also to preserve HRQoL ⁴. HRQoL is a multidimensional construct that covers the patients' perceptions of his or her physical, emotional, social, and cognitive functions. HRQoL assessment is an important aspect of cancer care. It gives a good overview of cancer patients' subjective experiences with cancer, its treatment, and follow-up procedures ⁵. Cancer survivors often deal with adaptation problems and assessment of their HRQoL could help to improve aftercare ⁶. The recent availability of recombinant human thyroid stimulating hormone (rhTSH or thyrogen) as a less burdensome alternative for thyroid hormone withdrawal in the follow-up procedure stimulated the research into the HRQoL of thyroid cancer patients. However, little is known about the impact of primary treatment and follow-up therapies on the HRQoL of (long-term) cancer survivors. The US National Coalition for Cancer Survivorship defines a person as a survivor from the moment of diagnosis through the balance of his or her life ⁷. The term 'long-term cancer survivors' refers to those who are living 5 years or more beyond a cancer diagnosis. The goal of this review is to provide a complete overview of the literature on the HRQoL of thyroid cancer survivors.

METHODS

Search strategy

A computerized search of the literature through the search engine Pubmed was performed on February 7, 2011. The search strategy combined the term 'thyroid cancer' or 'thyroid carcinoma' with other key terms: 'quality of life', 'QoL', 'health-related quality of life', 'HRQoL', 'health status' and 'well-being'. The reference lists of all identified publications were checked to retrieve other relevant publications. There were no restrictions with regard to the year of publication. The search yielded 371 hits.

Selection criteria

Studies that met the following criteria were included: (1) if the objective was to describe HRQoL of thyroid cancer patients (2) if the publication was an original article (3) if the article was a full report published in English and (4) if it was published in a peer-reviewed journal. Studies were excluded for the following reasons: (1) if the study focused on terminally ill patients (life expectancy of less than 6 months) or children with thyroid cancer (<18 years of age), (2) if the study focused on patients with other thyroid diseases such as hypothyroidism without having thyroid cancer or other cancers as head-neck cancer or nasopharyngeal cancer, (3) if the study focused on risk groups with a (genetic) predisposition for thyroid cancer, (4) if the study only described experienced symptoms instead of HRQoL outcomes (5) if the objective was to describe the relation of HRQoL with other variables such as mood states, without the description of HRQoL itself.

The described inclusion and exclusion criteria were applied to our initial 371 hits. Based on their titles and abstracts, 37 articles met our criteria. The hard copies were obtained and reviewed by two investigators (OH and LP). After careful review, 27 articles fulfilled our selection criteria and were included in this review. The flow-chart of this selection procedure is shown in Figure 1.

Quality assessment

The methodological quality of each of the selected articles was independently assessed by the two investigators based on established criteria for systematic reviews (Table 1) ⁸. Each item of a selected study, that matched our criteria, was assigned one point. If an item did not meet our criteria or was described insufficiently or not at all, zero points were assigned. The highest possible score was 12. Studies scoring 10 points or more were arbitrarily considered to be of 'high quality'. Studies scoring between 6 and 10 points were rated as 'adequate quality'. Studies scoring less than 6 points were considered to be of 'low quality'.

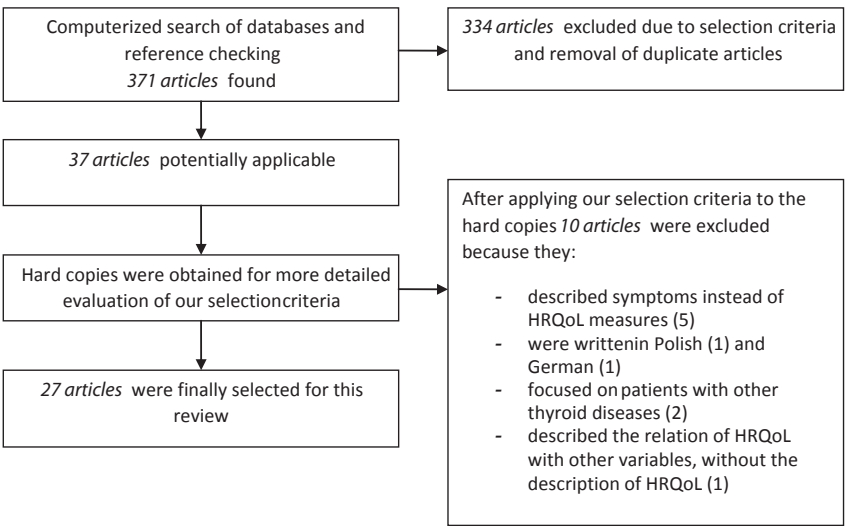


Figure 1: Flow-chart of selection procedure

Table 1: List of criteria for assessing the methodological quality of studies on quality of life of thyroid cancer patients

Positive if with respect to
<p>HRQoL assessment</p> <p>1. A valid (health-related) quality of life and/or health status questionnaire is used.</p>
<p>Study population</p> <p>2. A description is included of at least two socio-demographic variables (e.g., age, employment status, educational status).</p> <p>3. A description is included of at least two clinical variables of the described patient population (e.g., tumour stage at diagnosis).</p> <p>4. Inclusion and/or exclusion criteria are described.</p> <p>5. Participation and response rates for patient groups have to be described and have to be more than 75%.</p> <p>6. Information is given about the degree of selection of the patient sample (information is given about the ratio respondents versus non-respondents).</p>
<p>Study design</p> <p>7. The study size is consisting of at least 50 patients (arbitrarily chosen).</p> <p>8. The collection of data is prospectively gathered.</p> <p>9. The process of data collection is described (e.g., interview or self-report etc.).</p>
<p>Results</p> <p>10. The results are compared between two groups or more (e.g., healthy population, groups with different treatment or age) and/or results are compared with at least two time points (e.g., longitudinally versus post-treatment).</p> <p>11. Mean, median, standard deviations or percentages are reported for the most important outcome measures.</p> <p>12. Statistical proof for the findings is reported.</p>

RESULTS

Study characteristics

In total, 27 studies were included, all published between August 1997 and September 2010. HRQoL was the primary outcome in all studies. Eight studies focused on the impact of a specific treatment on HRQoL, 11 studies on the impact of follow-up procedures on HRQoL (3 of these also focused on some aspects of treatment) and 11 studies evaluated HRQoL among (long-term) cancer survivors. Prospective, cross-sectional, observational as well as intervention studies were included. The SF-36⁹ was the most frequently used HRQoL questionnaire. The main findings are summarized in Table 2.

Methodological quality

The evaluation of the methodological quality of the studies by the two reviewers yielded disagreement on 11 items (3.3%), mostly due to differences in interpretation. These were solved through discussion in a consensus meeting. The quality scores ranged from 2 to 12 points (Table 2) and the mean quality score was 8.8. One of the studies had a low quality according to our criteria and 10 studies had a high quality. The remaining 16 studies had an adequate quality. General shortcomings of the included studies were a lack of description of inclusion and/or exclusion criteria, response rates below 75%, a cross-sectional design, and a lack of information on the degree of selection of the patient sample. The studies will be discussed in order of their aim, starting with the effects of specific treatments and follow-up procedures on HRQoL, and ending with the HRQoL of (long-term) thyroid cancer survivors in general. Terminology is not consistent over the included articles, therefore 'HRQoL' is used throughout this manuscript to overcome illegibility.

Thyroid cancer treatments

Surgery

Three studies, two prospective^{10, 11} and one cross-sectional¹², focused on the effects of surgery on HRQoL of thyroid cancer patients.

The first prospective study showed that thyroid cancer patients who underwent (hemi) thyroidectomy had worse scores on social functioning, mental health and role limitation due to physical and emotional problems in comparison with the general population of the United States¹⁰. However, there was a trend towards recovery when time since surgery increased up to 12 months after operation. There were no differences in HRQoL scores between patients who underwent total thyroidectomy and patients who underwent hemithyroidectomy at any time point. The second prospective study demonstrated that postoperative HRQoL scores (12 months after surgery) on the domain of eating and emotional functioning, for patients who underwent tracheal resection for locally invasive thyroid cancer, were significantly

better than those of a comparison group composed of patients undergoing treatment for oropharynx cancer ¹¹. Baseline HRQoL scores were lacking in this prospective study.

In a cross-sectional study (patients' median time since treatment was 2 years), patients submitted to modified radical neck dissection reported worse chewing and shoulder scores than patients submitted to selective paratracheal lymph node dissection and patients who only underwent total thyroidectomy ¹². A mild dysfunction of the shoulder of patients undergoing neck dissection was also found in a study aimed to investigate HRQoL of long-term thyroid carcinoma survivors ¹³.

In summary, surgery for thyroid cancer leads to worse mental and physical HRQoL scores compared to the scores of the general population, however there is a trend towards recovery in time. The size of the effect of HRQoL depends on the type of surgery.

Radioiodine remnant ablation

Two randomized controlled trials focused on the effects of radioiodine ablation with or without recombinant human TSH (rhTSH) ^{14,15} on HRQoL. In both studies, HRQoL of euthyroid patients on L-thyroxine treatment receiving rhTSH was preserved compared to a drop in HRQoL for hypothyroid patients withdrawing L-thyroxine treatment to prepare for remnant ablation. In the Italian study, scores of seven of the eight scales of the SF-36 improved for the euthyroid group from baseline (within 14 days after thyroidectomy) to one month after ablation (week 4), while these same scores deteriorated for the hypothyroid group ¹⁴. In the French study, physical well-being, functional well-being, and fatigue were affected in the hypothyroid group at t1 (leaving the hospital after remnant ablation) compared to baseline (one day after thyroidectomy). However, HRQoL was preserved in the euthyroid patients after remnant ablation. After 3 (t2) and 9 months (t4), the groups were no longer statistically significant different on HRQoL ¹⁵.

A cross-sectional study found that postoperative radioactive iodine treatment was the most important predictor of HRQoL in patients with thyroid cancer, affecting the domains chewing, speech, taste, saliva and anxiety ¹². This study also concluded that patients who received higher doses (more than 150 mCi) of radioactive iodine reported significantly worse HRQoL compared to patients who received lower doses.

In summary, radioiodine remnant ablation affects some, mainly physical, domains of HRQoL, however rhTSH preserves HRQoL better than withdrawing levothyroxine treatment.

Thyroid hormone therapy

Four studies, three prospective ¹⁶⁻¹⁸ and one cross-sectional study ¹⁹, focused on the effects of lifelong thyroid hormone treatment on HRQoL.

The first prospective study found that patients under chronic suppressive levothyroxine treatment (chronic mild or subclinical hyperthyroidism) had an impaired HRQoL compared

with healthy age-matched controls ¹⁸. The total score and the emotional, sleep, energy and social scales of the Nottingham Health Profile and mental health, general health and social function of the SF-36 were lower in the thyroid cancer patient group at baseline (under usual levothyroxine dose). After 4 to 7 days of withdrawal of levothyroxine, necessary for whole body scanning, HRQoL scores were better than under levothyroxine treatment although one day before scanning (hypothyroid state) the HRQoL scores were worse.

In a randomized controlled trial it was investigated whether restoration to euthyroidism by decreasing levothyroxine dose improved HRQoL parameters. After 6 months, all HRQoL parameter values of the low TSH-group were the same as the baseline values. For the euthyroid group, only the role limitations as a result of physical problems (SF-36) deteriorated after 6 months ¹⁷. The authors concluded that restoration of euthyroidism in general does not affect HRQoL.

Another prospective study found that patients on thyroid hormone treatment, before rhTSH, were not significantly different from the US norm population on four of the eight SF-36 scales (physical functioning, vitality, social functioning and role emotional) and on the mental component scale. However, patients on thyroid hormone therapy scored better than the US norm population on two scales (role physical function and bodily pain) and the physical component scale whereas they scored worse on the general and mental health scale ¹⁶.

A cross-sectional study evaluated the effects of chronic suppressive doses of levothyroxine on HRQoL. Compared with the German general population, patients scored lower on seven of eight SF-36 domains (not bodily pain) and on the mental component scale ¹⁹. However, patients using levothyroxine scored better on physical functioning, role-physical, bodily pain, vitality and role-emotional scales and the mental and physical component scores compared to patients under short-term hypothyroidism ¹⁹.

In summary, levothyroxine treatment results in similar or slightly impaired HRQoL compared to the general population.

Thyroid cancer follow-up tests

Thyroid hormone withdrawal for Tg measurement and/or whole body scanning

Four prospective studies found a negative effect of thyroid hormone withdrawal on several aspects of HRQoL ^{18, 20-22}. The first study found a significant reduction of HRQoL from the week before the radioiodine scan to peak thyroid hormone withdrawal, while there was a gradual improvement from peak withdrawal to 4 weeks after the scan at normal levothyroxine therapy. The main differences in HRQoL between peak withdrawal and normal levothyroxine therapy were seen on the physical, psychological and social well-being scales, both for the thyroid specific HRQoL and the general HRQoL (FACT-G) ²⁰. Besides this, the second study also found a reduction in the spiritual domain between baseline (prior to withdrawal) and

after the 3 week withdrawal period. Four weeks after resumption of the thyroid hormone therapy the HRQoL domains were similar to baseline levels ²¹. The third prospective study found that HRQoL worsened with the time of levothyroxine withdrawal. In the first 2 weeks of levothyroxine withdrawal there was a significant worsening of the physical domain and total HRQoL score of the FACT-G, and additionally after 4 weeks of withdrawal the emotional and social domains were also significantly affected compared with the start of withdrawal ²². Another study found that patients in profound hypothyroidism after withdrawing levothyroxine treatment for whole body scanning had worse scores on all HRQoL indexes of the SF-36 and Nottingham Health Profile compared to euthyroid controls ¹⁸.

One prospective study searched for HRQoL effects of a short (3 week) levothyroxine withdrawal instead of a long (4 weeks) levothyroxine withdrawal for thyroglobulin screening. There was a significant reduction in 6 of the 8 HRQoL scales of the SF-36 (physical function, role-physical, vitality, social function, role-emotional and mental health) from the time of withdrawal to the time of peak TSH. Four weeks after resumption of levothyroxine therapy HRQoL returned to prewithdrawal levels for all categories. In comparison with the general population SF-36 scores, except vitality, did not fall below 50% of the general population scores ²³.

A qualitative cross-sectional study found that changes in physical well-being due to withdrawal from thyroid hormone medication influenced psychological and social well-being ²⁴. The other two cross-sectional studies evaluated the effects of short-term hypothyroidism in patients hospitalized for radioiodine therapy or whole body scanning ^{5,19}. The hypothyroid patients scored worse in seven of eight domains of the SF-36 in the first study ¹⁹ and on all domains in the second study compared with the German general population ⁵. The mental component score of the SF-36 was also significantly lower in both studies for the hypothyroid patients and the physical component score was worse in the second study for the hypothyroid group.

In summary, thyroid hormone withdrawal causes significant reductions in physical and mental HRQoL. After resumption of the levothyroxine treatment HRQoL levels will return to prewithdrawal levels.

Thyroid hormone withdrawal vs. rhTSH for Tg measurement and/or WBS

Three prospective studies were conducted to assess HRQoL differences between rhTSH and thyroid hormone withdrawal in thyroglobulin measurement and/or whole body scanning ^{16, 25, 26}. The first prospective multicenter study found that after rhTSH administration, 7 of 8 domains of the SF-36 were at or above the level of the US reference group; only general health was significantly lower for the rhTSH group. In contrast, after hormone withdrawal the patients scored significantly worse on all 8 domains compared to the US reference group ¹⁶. The same was found in the other two studies where rhTSH patients reported significantly

better HRQoL scores on performance of physical activities, problems with daily activities as a result of physical health, bodily pain, and emotional problems compared to hypothyroid patients. The physical component score of the SF-36, but not the mental component score, was also higher for rhTSH patients ^{25, 26}.

In summary, the use of rhTSH instead of thyroid hormone withdrawal prevents HRQoL deterioration accompanied by the withdrawal.

Thyroid cancer survivors

Eleven studies, 2 prospective ^{27, 28} and 9 cross-sectional ^{13, 29-36}, focused on the HRQoL of (long-term) thyroid cancer survivors. One prospective study found no significant differences in SF-36 scores between thyroid cancer patients (14 years since the primary operation) and a healthy Swedish reference population ²⁷. However, the other prospective study found significant differences in HRQoL between patients with differentiated thyroid cancer (DTC) (diagnosed from < 1 to 23 years earlier) and a control group of subjects with non-toxic multinodular goiter (enlargement of the thyroid that is not associated with overproduction of thyroid hormone or malignancy) on levothyroxine therapy ²⁸. DTC patients scored worse on anxiety, depression, somatisation, hostility. A second evaluation with a subset of the thyroid cancer patients after 8-14 months showed a slight improvement in overall sum scores and on the somatisation scale.

Four cross-sectional studies found worse HRQoL scores for thyroid cancer survivors compared with healthy reference groups ^{29-31, 35}. Thyroid cancer patients (5 months - 27 years after diagnosis) had lower scores on all domains of the SF-36 except for social functioning compared to the general Singaporean population. Older patients (≥ 50 years) scored worse on physical functioning, higher educated patients (>12 years) scored better on mental health, and employed patients scored better on role physical emotional domains compared to their counterparts ²⁹. Compared with German reference values, patients with non-metastatic thyroid cancer under levothyroxine therapy (mean period since the diagnosis of thyroid cancer was 5.5 years) reported significantly lower vitality, role-physical, mental health, role-emotional and social functioning domains of the SF-36 during their first year after diagnosis. After this first year, the SF-36 domains increased correlating with the time since initial diagnosis, except for vitality and role-emotional functioning ³⁰. When compared with Dutch controls, selected by patients themselves, thyroid cancer survivors (median time after initial treatment was 6.3 years) scored worse on social functioning and general health of the SF-36. When compared with age- and gender-matched controls from other HRQoL-studies, physical functioning and role limitations due to physical problems were also negatively affected in the patient group. Better scores on the social functioning, role limitations due to physical problems and general health scales were correlated with a longer time since initial treatment ³¹. Disease-free survivors of DTC showed decreased

HRQoL compared with age-matched controls from the Korean general population on five functional domains (physical, role, cognitive, emotional and social) of the EORTC-QLQ-C30³⁵. A lower HRQoL was associated with higher scores on anxiety, depression and fatigue.

One cross-sectional study found no significant differences in total HRQoL scores on the 15D between thyroid cancer survivors (mean 12.4 years after initial treatment) and an age- and gender-standardized general Finnish population. The survivors scored worse on the sleeping, speech and distress domains of the 15D and better on the discomfort and symptom items compared to the general population. Older age at time of initial treatment was associated with worse HRQoL³².

Four cross-sectional studies without a reference group found that thyroid cancer survivors reported good long-term health³³ and scored very high on all domains of the EORTC-QLQ-C30³⁴, but also reported thyroid specific, lasting medical problems due to cancer and its treatment^{33,34}. The mean score of general health was 3.1 on a 5-point scale for patients who underwent total thyroidectomy¹³. This was lower than expected when compared with other forms of cancer. The last study found that fatigue, high impact of operational scar, and chills (cold intolerance) were negatively associated with HRQoL, while social support was positively correlated with HRQoL³⁶. Contradictory, they also showed that patients at 19-36 months after thyroidectomy had lower HRQoL scores compared with those patients within 18 months of operation³⁶.

In summary, (long-term) thyroid cancer survivors score similar or worse on HRQoL scales compared to the general population. Thyroid cancer survivors report some specific long-lasting problems.

DISCUSSION

Thyroid cancer survivors report severe (long-term) impairments of HRQoL after treatment and follow-up procedures. Surgery had a negative impact on short-term HRQoL scores, but HRQoL scores recovered when the time since surgery increased. Based on one study, no differences were found between total thyroidectomy and hemithyroidectomy, more research is needed. The exact influence of surgery on HRQoL cannot be determined, because most patients received radioiodine shortly after the operation which distorts the influence of surgery. Lifelong thyroid hormone therapy can lead to slightly impaired HRQoL scores, this impairment was not found in studies with higher quality. HRQoL was most affected during thyroid hormone withdrawal for radioiodine remnant ablation or follow-up procedures. The use of rhTSH instead of hormone withdrawal leads to considerable improvements in HRQoL during follow-up testing.

Table 2: Included studies, summarized in order of their aim

Author, year, country [ref]	Design	Patients	Treatment	Outcome measures	Conclusion authors	Quality score
Surgery						
Shah, 2006, United States ¹⁰	Prospective	76 well-differentiated thyroid carcinoma (WDTC)	<ul style="list-style-type: none"> - All hemithyroidectomy or thyroidectomy - 13.1% neck dissection - 83.3% RAI ablation therapy - 7.1% external beam radiotherapy 	SF-36 Thyroid QoL scale (City of Hope)	HRQoL impaired in comparison with general population. HRQoL is not significantly impacted by the extent of surgery.	11
Sywak, 2003, Canada ¹¹	Prospective	7 patients with locally invasive thyroid cancer	Thyroidectomy and resection of some part of the upper aerodigestive tract	Head and Neck cancer specific HRQoL questionnaire	Function and HRQoL after resection of some part of the upper aerodigestive tract are acceptable.	10
Almeida, 2009, Brazil ¹²	Cross-sectional	154 DTC patients with stage I or II tumors	<ul style="list-style-type: none"> - All total thyroidectomy - 38 (24.7%) neck dissection - 93 (60.4%) RIT 	UW-QOL	Neck dissection affected chewing and shoulder scores.	8
Radioiodine remnant ablation						
Pacini, 2006, Italy ¹⁴	Prospective	63 patients with DTC	Thyroidectomy: <ul style="list-style-type: none"> - euthyroid group (33), which received rhTSH to prepare for radioiodine therapy - hypothyroid group (30), thyroid hormone treatment was withheld before radioiodine therapy 	SF-36 Billewicz scale	HRQoL was well preserved in the euthyroid group, compared with the hypothyroid group.	12
Taieb, 2009, France ¹⁵	Prospective	74 well-differentiated papillary or follicular carcinoma patients	-All total thyroidectomy <ul style="list-style-type: none"> - 26% lymph node dissection - levothyroxine was initiated in both groups: discontinued in the hypothyroid group and continued in the rhTSH group 	FACIT-F including FACT-G	rhTSH preserves HRQoL of patients undergoing radioiodine remnant ablation with similar rates of ablation success compared to hypothyroidism.	12
Almeida, 2009, Brazil ¹²	Cross-sectional	154 DTC patients with stage I or II tumors	<ul style="list-style-type: none"> - All total thyroidectomy - 38 (24.7%) neck dissection - 93 (60.4%) RIT 	UW-QOL	Patients submitted to radioactive iodine therapy at doses higher than 150 mCi are at risk for poor HRQoL.	8

Table 2: Included studies, summarized in order of their aim (Continued)

Author, year, country [ref]	Design	Patients	Treatment	Outcome measures	Conclusion authors	Quality score
Thyroid hormone therapy						
Botella-Carretero, 2003, Spain ¹⁸	Prospective	18 women with DTC	-Initial thyroidectomy and radioactive iodine ablation; - Chronic suppressive doses of levothyroxine	SF-36 NHP	HRQoL in patients with DTC is affected by long-term treatment with supraphysiological doses of levothyroxine.	6
Eustatia-Rutten, 2006, the Netherlands ¹⁷	Prospective	24 subjects with a history of DTC	-Initial total thyroidectomy and radioiodine ablative therapy -12 patients TSH suppressive therapy (low TSH-group) -12 patients restoration of euthyroidism by decreasing L thyroxine dose (euthyroid group)	SF-36	HRQoL in patients with DTC and long-term subclinical hyperthyroidism is preserved. Restoration of euthyroidism does not affect HRQoL.	11
Tagay, 2005, Germany ¹⁹	Cross-sectional	Group2: 100 DTC out-patients under TSH-suppressive doses of levothyroxine subsequent to radioiodine therapy	Total thyroidectomy	SF-36 Hypothyroid physical complaints scale	Patients under TSH-suppressive doses of levothyroxine subsequent to radioiodine therapy had a significantly impaired HRQoL.	9
Schroeder, 2006, United States ¹⁶	Prospective	229 patients with thyroid carcinoma (papillary, follicular, hurthle cell, papillary/follicular)	-Total or near total thyroidectomy -80% radioiodine ablation - Effect of recombinant human thyrotropin compared with thyroid hormone withdrawal	SF-36	Patients on thyroid hormone treatment had similar SF-36 scores as the US norm population on 5 scales, scored better on 2 scales (role-physical, pain) and worse on 2 scales (general, mental health).	9
Follow-up: Thyroid hormone withdrawal for thyroglobuline measurement and/or whole body scanning						
Golger, 2003, Canada ²³	Prospective	181 patients with well-DTC	Bilateral surgical thyroidectomy followed by RAI ablation therapy	SF-36	Overall degree of functional impairment was not severe and did not result in loss of employment time.	10

Table 2: Included studies, summarized in order of their aim (*Continued*)

Author, year, country [ref]	Design	Patients	Treatment	Outcome measures	Conclusion authors	Quality score
Dow, 1997, United States ²⁰	Prospective	34 thyroid cancer patients	No information about treatment, except for thyroid hormone withdrawal in preparation for scanning procedures	QOL-thyroid questionnaire (Dow et al., 1997) FACT-G	Significant better physical, psychological, and social well-being occurred at levothyroxine therapy compared with peak hormone withdrawal.	8
Davids, 2006, Canada ²¹	Prospective	181 patients with well-DTC	-Previously treated with total or near-total thyroidectomy and one or more doses of radioactive iodine ablation therapy -Impact of 3-week instead of 6-week levothyroxine withdrawal test	QOL-thyroid questionnaire (Dow et al., 1997)	A small reduction in HRQOL of thyroid cancer patients undergoing an induced 3-week hypothyroid state was found.	9
Chow, 2006, China ²²	Prospective	78 patients with DTC	-Previous total or near-total thyroidectomy and radioactive iodine (RAI) treatment -Levothyroxine withdrawal 4 weeks before whole body scanning (WBS)	FACT-G	HRQOL declines with time of levothyroxine withdrawal. The impact is more severe in the later period of levothyroxine withdrawal.	9
Botella-Carretero, 2003, Spain ¹⁸	Prospective	18 women with DTC	-Initial thyroidectomy and radioactive iodine ablation; - Chronic suppressive doses of levothyroxine - Levothyroxine withdrawal	SF-36 NHP	HRQOL in patients with DTC is affected by withdrawal of levothyroxine.	6
Tagay, 2005, Germany ¹⁹	Cross-sectional	Group 1: 130 DTC patients hospitalized for radioiodine therapy or whole-body diagnostics under short-term hypothyroidism	Total thyroidectomy	SF-36 Hypothyroid physical complaints scale	The hypothyroid patients scored worse in seven of eight domains of the SF-36 and the mental component score compared with the German general population.	9
Tagay, 2006, Germany ⁵	Cross-sectional	136 DTC patients hypothyroid on thyroid hormone withdrawal hospitalized for radioiodine administration	Thyroidectomy and thyroid hormone withdrawal	SF-36	HRQOL is severely impaired in DTC patients under short-term hypothyroidism.	10
Dow, 1997, United States ²⁴	Cross-sectional	34 thyroid cancer patients who had undergone thyroid hormone withdrawal before body scanning	Thyroid hormone withdrawal	Three open-ended questions about quality of life during hormone withdrawal	Changes in physical well-being due to hormone withdrawal coupled with the potential for disease recurrence influenced psychological and social well-being.	2

Table 2: Included studies, summarized in order of their aim (*Continued*)

Author, year, country [ref]	Design	Patients	Treatment	Outcome measures	Conclusion authors	Quality score
Follow-up: Thyroid hormone withdrawal versus rTSH for Tg measurement and/or whole body scanning						
Ladenson, 2002, United States²⁵	Prospective	Protocol II: 220 patients with differentiated epithelial thyroid cancers (papillary, follicular, and Hurthle cell cancers)	-Thyroidectomy -Thyroid hormone treatment	SF-36	After rTSH administration and thyroid hormone withdrawal, patients showed significantly higher physical component, but not mental component scores with rTSH compared to hormone withdrawal.	6
Schroeder, 2006, United States¹⁶	Prospective	229 patients with thyroid carcinoma (papillary, follicular, hurthle cell, papillary/follicular)	-Total or near total thyroidectomy -80% radioiodine ablation - Effect of recombinant human thyrotropin compared with thyroid hormone withdrawal	SF-36	Short-term hypothyroidism after levothyroxine withdrawal is associated with a significant decline in HRQoL that is abrogated by rTSH use.	9
Haugen, 1999, United States²⁶	Prospective	229 patients with DTC requiring radioiodine whole body scan	All but 1 patient had undergone a total or near total thyroidectomy, and 83% had received prior radioiodine therapy	SF-36 Billewicz scale	Patients reported better HRQoL scores after rTSH administration compared with thyroid hormone withdrawal.	8
Thyroid cancer survivors						
Malterling, 2010, Sweden²⁷	Prospective	130 DTC patients treated with surgery (52 filled in the SF-36)	- Subtotal or total thyroidectomy -56% received postoperative radioiodine ablation	SF-36	Mental and physical HRQoL among patients treated for DTC were similar to the healthy population.	9
Giusti, 2005, Italy²⁸	Prospective	61 patients with a history of DTC	All but one patient had previously undergone near-total thyroidectomy and radioiodine treatment.	KSQ	DTC patients scored worse on all KSQ scales compared to a control group of subjects with non-toxic multinodular goiter on LT-4 therapy.	9
Tan, 2007, Singapore²⁹	Cross-sectional	290 consecutive patients with well-differentiated thyroid cancer	90% had surgical intervention, with 84% requiring radioiodine treatment.	SF-36	There is a significant decrease in HRQoL, especially in the elderly and poorer educated.	9

Table 2: Included studies, summarized in order of their aim (Continued)

Author, year, country [ref]	Design	Patients	Treatment	Outcome measures	Conclusion authors	Quality score
Crevenna, 2003, Austria 30	Cross-sectional	150 consecutive patients with DTC	Total thyroidectomy - Radioiodine ablation, - Under current levothyroxine treatment	SF-36	Findings indicate that vitality, role-physical, mental health, role-emotional and social functioning are significantly impaired during the first year after diagnosis. Thereafter, HRQoL improves but vitality and role-emotional remain permanently impaired.	
Hofstijzer, 2008, the Netherlands 37	Cross-sectional control study	153 cured DTC patients with median duration of cure of 6.34 years	Initial therapy consisted of near-total thyroidectomy, followed by postoperative radioiodine ablation therapy with I-131	SF-36 SDQ	Patients cured for DTC have impaired HRQoL parameters independently of TSH level. HRQoL parameters were inversely affected by duration of cure.	10
Lee, 2010, Korea 35	Cross-sectional	316 disease-free survivors of DTC	Total thyroidectomy (89.9%) and subtotal thyroidectomy or hemithyroidectomy (10.1%); RAI treatment in 92% of the patients	EORTC-QLQ-C30	Decreased HRQoL for disease-free survivors of DTC in physical, role, cognitive, emotional and social domains compared to age-matched healthy control group.	11
Pelttari, 2009, Finland 32	Cross-sectional	341 cured TNM stage I or II DTC survivors	The majority of patients underwent a near total thyroidectomy (98.8%), postoperative radioiodine ablation (84.5%) and TSH suppressive levothyroxine therapy as primary treatment.	15D	After long-term follow-up, overall HRQoL in DTC patients is comparable to that of the general population. DTC patients demonstrate an age-related decline in HRQoL, similar to that seen in the population in general.	10
Roberts, 2008, United States 34	Cross-sectional	62 patients with thyroid cancer	-	EORTC-QLQ C30 Thyroid QoL scale (City of Hope)	Results indicate that HRQoL is generally quite high in this population. Thyroid-specific problems were relatively low.	7

Table 2: Included studies, summarized in order of their aim (Continued)

Author, year, country [ref]	Design	Patients	Treatment	Outcome measures	Conclusion authors	Quality score
Schultz, 2003, United States ³³	Cross-sectional	518 thyroid cancer survivors	All had surgery and 80.5% also had some radiation	Self developed: -Do you believe that having cancer has affected your overall health? -Checklist: which specific health conditions and/or effects they have experienced?	Thyroid cancer survivors generally report good health long-term but describe distinct, lasting medical problems including symptoms of thyroid dysregulation.	7
Dagan, 2004, Israel ¹³	Cross-sectional	78 patients with well-DTC	Total thyroidectomy	UW-QOL for head and neck cancer with specific domains associated with thyroid disease	HRQOL in DTC patients was good although lower than expected when compared with other forms of cancer.	7
Huang, 2004, Taiwan ³⁶	Cross-sectional	218 patients who had thyroidectomy for thyroid cancer	Thyroidectomy	Chinese version QLI	HRQOL scores among thyroid cancer patients after operation are similar to those among people with chronic conditions.	9

DTC = differentiated thyroid cancer; SF-36 = Short Form 36; FACT-G = Functional Assessment in Cancer Therapy – General; EORTC-QLQ C30 = European Organization for Research and Treatment in Cancer-Quality of Life Questionnaire C30; SDQ = Somatoform disorders questionnaire; KSQ = Kellner Symptoms Questionnaire; NHP = Nottingham Health Profile; UW-QOL = University of Washington Quality of Life questionnaire ; QLI = Quality of life Index; FACT-F = Functional assessment of chronic illness therapy-fatigue

Studies that focused on (long-term) thyroid cancer survivors showed contradictory results. While most patients report some specific long-lasting health problems, most high quality studies found a lower HRQoL for thyroid cancer survivors compared with a healthy population or other reference groups, whereas lower quality studies found no differences with the normal population. However, long-term survivorship studies are lacking and also the influence of developing a metastasis on HRQoL is underreported. Comparison of the results of the included survivorship studies using the SF-36 as HRQoL questionnaire ^{27, 29-31}, with data from studies with patients with chronic disorders showed that thyroid cancer survivors reported better HRQoL scores on all SF-36 subscales compared to patients with chronic heart failure, chronic obstructive pulmonary disease, fibromyalgia and depression ³⁸⁻⁴⁰. Thyroid cancer survivors scored better or similar on the physical scales (physical functioning, bodily pain, general health, role-physical) and worse on vitality and the mental scales (social functioning, role-emotional, mental health) compared to diabetes mellitus patients ^{39, 41}.

The results of the studies discussed in this review should be handled with caution. Most included studies were of adequate quality. However there were several methodological issues that impede drawing strong conclusions on the HRQoL of thyroid cancer survivors. First, there is a lack of a valid, thyroid cancer specific instrument to assess HRQoL ^{12, 42}. Most studies used a general HRQoL questionnaire, which cannot capture the specific complaints associated with thyroid cancer and its treatment. Also, many different questionnaires were used to assess HRQoL which makes it difficult to compare the results of the different studies. Other problems were small sample sizes (less than 100 patients) ^{10, 11, 13-15, 17, 18, 20, 22, 24, 28, 34}, lack of (healthy) control groups ^{12, 13, 20-24, 34, 36} and use of cross-sectional designs ^{5, 12, 13, 19, 24, 29-34, 36}. Most studies focused on survivors between 1 and 5 years after diagnosis while the negative effects of cancer and its treatment can still fluctuate years thereafter.

The diagnosis and treatment of thyroid cancer significantly impacts the lives of survivors ⁴³. Radical surgical treatment and toxicities of treatment can create chronic long-term health problems and late effects like vocal cord paralysis, hoarseness, fatigue, insomnia, chills (cold intolerance), tetany and tingling around the mouth ³⁶. Because the thyroid gland is (partially) removed, most health problems are endocrine related and caused by the hyper- and hypothyroid states. Frequently reported symptoms are peripheral edema, difficulty concentrating, memory loss, insomnia, intolerance of cold, temperature sensitivity, weight gain, sleep disturbances, skin dryness, muscle cramping, constipation, hoarseness, slow movements, anxiety, puffy face and hands, and loss of libido ^{3, 19, 44}. The fluctuating thyroid hormone levels could cause the different results for the effect of levothyroxine on HRQoL. Some patients experience hyperthyroid symptoms accompanied by more energy and better well-being, while others experience more hypothyroid symptoms accompanied by more

negative distress and worse well-being. It is important for patients to undergo regular medical check-ups, not only to check the recurrence status, but also to adapt the dose of levothyroxine. The use of rhTSH in follow-up care led to a reduction in health problems and consequently maintenance of HRQoL. The recent trend in management of thyroid cancer towards individualizing treatment and avoiding aggressive interventions in low risk cases ⁴⁵ is expected to have a positive impact on HRQoL of thyroid cancer survivors.

Besides direct treatment and follow-up related effects, HRQoL can also be affected negatively by fear and uncertainty related to a cancer diagnosis, feelings of diagnosis being dismissed as not seriously or “having a good cancer (prognostically)”, receiving conflicting messages, or even no information about treatment-related side-effects ⁴³. There is a need for multidisciplinary after care leading to an improved HRQoL ³⁰. The first step for multidisciplinary after care will be recognition, recording and acknowledgment of specific (long-term) health problems of thyroid cancer patients by both primary and secondary health care professionals. Thereafter, development and evaluation of effective interventions is needed to address the needs of thyroid survivors. These interventions should not only be directed to adequate management of long-term problems, but also to adequate information provision. Thyroid patients perceive their illness on a subjective, emotional basis unrelated to its actual severity therefore inclusion of a psychologist in the multidisciplinary team could help to improve illness representations ⁴⁶. Another good opportunity would be the implementation of a survivorship care plan ⁴⁷, which aims at providing a cancer survivor with a summary of their course of treatment, management of late effects, and strategies for health promotion. Another component of such a plan is an ongoing care plan so that cancer survivors receive coordinated care from team members knowledgeable about the disease process and treatment-related side-effects.

Concluding, thyroid cancer has a big impact on survivors and multidisciplinary monitoring is therefore recommended. Future studies on HRQoL in thyroid cancer survivors should be prospective in design, include larger number of participants and include a thyroid cancer specific HRQoL questionnaire.

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CHAPTER 10

Development of a disease-specific health-related quality of life questionnaire (THYCA-QoL) for thyroid cancer survivors

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ABSTRACT

Background: To date, no valid instrument is available that focuses on specific health-related quality of life (HRQoL) issues that affect thyroid cancer survivors. Objective of this study was to develop and pretest a thyroid cancer specific HRQoL questionnaire that can be used in addition to the more general European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30).

Material and methods: Potentially relevant issues were identified by a systematic literature review, a focusgroup meeting, and an issue list completed by 6 health care professionals (HCP) and 18 thyroid cancer survivors. Resultant issues were analyzed on importance and relevance (Phase I). The issues were formulated into a long provisional list of questions (Phase II). These questions were administered in combination with the EORTC QLQ-C30 to 306 Dutch thyroid cancer survivors to pretest the hypothesized scale structure (Phase III). Although the development of this questionnaire was not set up as an international study, phase I-III are in agreement with the methodology of the EORTC guidelines.

Results: The literature search, focusgroup and issue list completed by HCP and survivors resulted in 75 issues. These were reduced to create a 30 item provisional list. Pretesting led to a selection of 24 items with a good range of response. This resulted in the THYCA-QoL containing 24 items and seven conceptual scales.

Conclusion: The THYCA-QoL in combination with the EORTC QLQ-C30 is ready for a large (international) scale validation study, and will assess HRQoL issues of most relevance and concern for thyroid cancer survivors.

INTRODUCTION

The incidence of thyroid cancer is rising worldwide ¹. Since the mortality rate of patients suffering from differentiated thyroid cancer remains relatively stable, and survival rates are high (5-year survival rates around 97% in 2007)², the number of thyroid cancer survivors is growing. In the United States in 2007, over 430,000 people have a history of thyroid cancer ^{2,3}. Treatment of thyroid cancer mostly involves surgery, predominantly total thyroidectomy with or without lymphadenectomy, followed by radioiodine treatment to ablate the remaining thyroid tissue ⁴. Dependent on staging of the thyroid cancer hemithyroidectomy could suffice. These aggressive surgical and postoperative treatments are associated with long-term physical and psychological morbidity ⁵. The removal of the whole thyroid gland is accompanied by a lifelong dependence on pharmacotherapy with thyroid hormone (levothyroxine) with dosing regimes suppressing TSH production. Despite the efficacy of these primary treatments and the high long-term survival rates, the disease has the potential to recur even decades later. Therefore, intensive long-term periodical follow-up, is necessary and associated with physical and psychological discomfort. In case of recurrence, additional radioiodine treatment or surgery is indicated. The treatment and follow-up care procedures impose great challenges on thyroid cancer survivors and could affect their health-related quality of life.

Health-related quality of life (HRQoL) is a multidimensional construct that covers the patients' perceptions of his or her physical, emotional, social, and cognitive functions. HRQoL gives a good overview of cancer patients' subjective experiences on cancer and its treatment and follow-up procedures ⁶. Cancer patients often deal with adaptation problems. Assessment of their HRQoL could help to improve aftercare ⁷. However, to date little is known about the impact of primary treatment and follow-up therapies on the HRQoL of thyroid cancer survivors. The US National Coalition for Cancer Survivorship defines a person as a survivor from the moment of diagnosis through the balance of his or her life ⁸. The long-term HRQoL of thyroid cancer survivors is also underexposed. A recent systematic review indicated that thyroid cancer survivors generally have a similar or slightly worse HRQoL compared to the normative population ⁹. Nevertheless, thyroid cancer survivors do report some specific medical problems during and after cancer treatment and follow-up tests which have a direct negative impact on their current HRQoL and could possibly affect their long-term HRQoL ⁹. The main problem of previous studies is the lack of a valid, specific instrument to assess the HRQoL of thyroid cancer survivors. Most studies used a general HRQoL questionnaire, which cannot unveil specific thyroid cancer related complaints. In a limited number of studies, some thyroid cancer specific items were added to a more general HRQoL questionnaire ¹⁰⁻¹³. However, these items were never validated, nor do they cover the whole spectrum of

health problems associated with thyroid cancer. The European Organization for Research and Treatment of Cancer (EORTC) developed a core cancer quality of life questionnaire (EORTC QLQ-C30) consisting of 30 items ¹⁴. The core questionnaire was intended to be supplemented by additional modules to assess specific disease and treatment related quality of life issues in particular patient groups ¹⁵. To the best of our knowledge, no module existed for thyroid cancer, nor did any other validated disease-specific questionnaire exist for this patient population.

Aim of this study was to develop a thyroid cancer specific HRQoL questionnaire applicable in combination with the core measure (EORTC QLQ-C30), in order to assess treatment and cancer specific side-effects of thyroid cancer. We describe the first three out of four phases of the development of a thyroid cancer specific module to supplement the EORTC QLQ-C30.

MATERIAL AND METHODS

Study design

Preparation and development of the thyroid cancer specific HRQoL questionnaire followed the guidelines published by the EORTC QOL Group for phase I-III ¹⁵⁻¹⁷, however our questionnaire is not an EORTC QOL group product and the development of this questionnaire was not set up as an international study. The module development process has four distinct phases, aimed at ensuring validity and reliability.

Phase I:

Phase I was aimed at compiling an exhaustive list of relevant HRQoL issues for thyroid cancer survivors. Extensive literature searches through PUBMED (February 2010) were conducted to identify all relevant HRQoL issues using the keywords: “quality of life”, “health-related quality of life”, and “complaints” in addition to “thyroid cancer” or “thyroid carcinoma”. The retrieved provisional list with issues was then translated into Dutch.

A focus group with thyroid cancer survivors (N=4) was composed in order to discuss relevant HRQoL issues in general, with respect to their phase of disease. An estimation of the impact of these issues to the survivors was explored. With this information issues that were lacking in the provisional list were added to this list. The provisional list was then presented to health care providers (HCP; N=6) for feedback on appropriateness of content and breadth of coverage. Missing issues were added to the list. The health care providers were asked to rate the issues from 1 (not relevant for thyroid cancer survivors) to 4 (very relevant for thyroid cancer survivors) on a Likert scale (relevance rating) and to select the 25 core issues which must be definitely included in the questionnaire (priority rating). The same was asked to a diverse group of thyroid cancer survivors (N=18). Issues with high relevance ratings

(mean score ≥ 1.5) for both health care providers and survivors and high priority ratings for inclusion in the module (ratings $\geq 25\%$) for both health care providers and survivors were added to the final list of issues.

Phase II:

The final list of HRQoL issues was operationalised into questions compatible with the EORTC QLQ-C30 in terms of format (response categories: 'not at all', 'a little', 'quite a bit' and 'very much') and time frame (one week for all items, except four weeks for the sexuality items). Where possible, issues which had been constructed into items in previous EORTC modules were used or adapted to provide comparability of data. This was done using the EORTC QOL Item Bank¹⁸, which comprises all existing EORTC QOL questionnaire items and their translations¹⁹.

Phase III:

Phase III of the module development was divided into two parts. In the first part the final list was pretested in a group (N=8) of thyroid cancer survivors (who did not participate in phase I). The objective was to identify problems relating to the phrasing and clarity of items. Survivors were asked to complete the EORTC QLQ-C30 and the thyroid specific items and underwent cognitive debriefing, indicating if they found any questions annoying, confusing, upsetting or intrusive, and if so, they were asked to re-phrase the question. Survivors were asked whether or not questions were irrelevant or additional issues should be included in the module. The questionnaire was adapted to the responses on these debriefing questions. In the second part of phase III, the resultant final questionnaire was pretested in a sample of survivors (N=306) to test the scale structure.

Statistical analyses

Descriptive statistics were used to calculate relevance and priority ratings of the issue list of phase I and to analyze the debriefing questions of the first part of phase III. For the second part of phase III, item descriptive statistics and the response distributions for each item were calculated, in order to examine central tendency, variability and symmetry.

To support construct validity, factor analysis was used to determine the underlying constructs, which explain significant portions of the variance. The factor loadings were examined in order to explain the meaning of each construct.

Multi-trait scaling analysis was employed to confirm the scale structure (found after exploratory factor analyses) of the questionnaire. To test for item-scale convergent validity, correlations of 0.40 or greater were sought between an individual item and its scale, corrected for overlap. Item-scale discriminant validity was examined by comparing the correlation of each item with its own scale versus other scales. An item was expected to

correlate significantly higher with its own scale than with other scales.

Additionally, reliability was tested via Cronbach's alpha coefficients, which ranges between 0 and 1. The higher the score, the more reliable the generated scale is. A minimum score of 0.70 is preferred ²⁰. Furthermore, convergent and divergent validity was examined by evaluating Pearson's correlations between the various scales of the EORTC QLQ-C30 and found scales of the thyroid cancer specific questionnaire. It was expected that scales that are conceptually related correlate moderately to highly with one another ($r \geq 0.40$). Conversely, scales with a less conceptual relation are expected to show weak correlations ($r < 0.40$) ²⁰. All analyses were performed using SPSS software, version 17.0 (SPSS Inc., Chicago IL)

RESULTS

Phase I:

Twenty-seven papers on HRQoL of thyroid cancer survivors were identified ⁹, and one non-validated thyroid cancer specific questionnaire was identified ¹⁰. This non-validated questionnaire did not cover the whole spectrum of health problems associated with thyroid cancer because it only added four thyroid cancer specific items to a more general HRQoL questionnaire for cancer survivors. A list of 64 relevant issues related to thyroid cancer was derived from these 27 articles. The focusgroup with four thyroid cancer survivors (mean age of 53 years, 2-19 years since diagnosis, 3 survivors with differentiated thyroid carcinoma and 1 with medullary thyroid carcinoma) resulted in 11 additional issues relevant for thyroid cancer survivors.

The rating (mean scores, range, prevalence and proportions of priority ratings) of the 75-issues by health care providers (N=6; three internist-endocrinologists, two surgeons and one MD specialized in nuclear medicine) and 18 thyroid cancer survivors (mean age of 49 years, 1-18 years since diagnosis, all differentiated thyroid cancer) resulted in removal of 37 issues. Additionally, eight issues of the remaining 38 issues were already covered by the EORTC QLQ-C30 (sleeping troubles (item 11), constipation (item 16), tiredness (item 18), difficulty concentrating (item 20), irritability (item 23), difficulty with remembering (item 25), troubles with family life (item 26), troubles in social life (item 27). This resulted in a list of 30 issues, relevant for thyroid cancer survivors.

Phase II:

A provisional questionnaire of 30 thyroid cancer specific items was constructed. Seventeen existing items from the EORTC QOL Item Bank (comprising all items used in disease-specific modules of EORTC QLQ-C30) were used and 13 new items were created.

Phase III:

Eight survivors reviewed the 30 items for clarity of wording and overlapping of items (debriefing questions), none of the items was excluded. The time for survivors' self completion of the EORTC QLQ-C30 and provisional thyroid cancer module was ≤ 10 minutes for four survivors (50%), between 11 and 15 minutes for three survivors (37.5%) and > 15 minutes for one survivor.

Table 1: Thyroid cancer patient characteristics (n=306)

Age at time diagnosis - Mean(SD)	46.3 (14.9)
Age at time of survey - Mean(SD)	56.4 (14.5)
Years since diagnosis - Mean(SD)	9.6 (5.5)
25 th percentile	4.7
Median	9.0
75 th percentile	13.5
Gender	
Male	76 (24.8%)
Female	230 (75.2%)
Tumour type	
Papillary and/or mixed papillary/follicular	217 (70.9%)
Follicular (including Hurthle cell)	73 (23.8%)
Medullary	13 (4.2%)
Other	1 (0.3%)
Stage at diagnosis	
I	172 (57.5%)
II	59 (19.7%)
III	48 (16.1%)
IV	20 (6.7%)
Primary treatment	
Surgery	83 (27.1%)
Surgery + radioiodine treatment	212 (69.3%)
Surgery + radiotherapy	9 (2.9%)
Other (chemotherapy/radiotherapy or no oncological treatment)	2 (0.7%)
Comorbidity	
None	68 (22.2%)
1	70 (22.9%)
>2	168 (54.9%)
Marital status	
Married/living together	238 (77.8%)
Divorced	25 (8.2%)
Widowed	31 (10.1%)
never married/lived together	12 (3.9%)
Educational level	
University	80 (26.2%)
Intermediate school	129 (42.3%)
Secondary school	63 (20.7%)
Primary school	33 (10.8%)
Current occupation	
Employed	154 (51.3%)
Not employed	146 (48.7%)

The EORTC QLQ-C30 and the provisional thyroid cancer specific list were completed by 306 survivors (Table 1). Response information is provided in Table 2, which displays the items descriptive statistics. Valid responses were high for all items. Six items with >80% of the answers falling in one answer category (floor effects) were excluded for factor analysis (different taste (item 6), trembling hands (item 13), cramps in arms (item 14), hair loss (item 19), hyperactivity (item 27), and depressive feelings (item 29)).

Table 2: Item descriptive statistics of 306 thyroid cancer survivors

Item	Description	Valid (%)	Mean (SD)	Distribution of valid responses (%)			
				1	2	3	4
1	Have you had a dry mouth?	98	1.5 (0.8)	63	27	6	4
2	Have you had trouble swallowing?	97	1.3 (0.6)	74	21	3	2
3	Have you been hoarse?	97	1.3 (0.6)	76	19	3	1
4	Have you had a weak voice?	97	1.4 (0.7)	72	20	6	2
5	Have you had a lump in your throat?	97	1.3 (0.7)	74	19	6	1
6	Did food and drink taste different as normal? *	97	1.1 (0.5)	89	9	1	1
7	Did the scar in your neck bother you?	97	1.3 (0.7)	78	15	3	3
8	Have you felt chilly?	97	1.8 (0.9)	48	33	10	9
9	Have you had difficulty tolerating heat?	97	1.5 (0.8)	66	20	11	3
10	Have you had hot flushes?	97	1.6 (0.9)	60	25	9	6
11	Have you had pain in your muscles and/or joints?	97	2.0 (1.0)	36	36	19	10
12	Have you had tingling hands and/or feet?	97	1.5 (0.8)	67	23	6	4
13	Have you had trembling hands?*	97	1.2 (0.6)	83	12	3	1
14	Have you had cramps in your arms?*	96	1.2 (0.6)	84	12	3	1
15	Have you had cramps in your legs?	97	1.6 (0.8)	57	26	14	3
16	Have you felt slowed down?	97	1.5 (0.7)	63	26	8	2
17	Have you gained weight?	96	1.3 (0.6)	71	26	3	1
18	Have you had painful, irritated or dry eyes?	96	1.4 (0.7)	67	24	6	3
19	Have you had hair loss?*	96	1.3 (0.6)	80	15	4	1
20	Have you had skin problems (e.g. itchy, dry)?	96	1.5 (0.7)	66	26	6	3
21	Have you suffered from palpitations?	96	1.3 (0.6)	74	20	5	1
22	Have you had headaches?	96	1.5 (0.7)	59	30	10	2
23	Have you had abrupt attacks from tiredness?	96	1.7 (0.9)	50	30	17	3
24	Have you had troubles with thinking?	96	1.5 (0.7)	59	32	7	2
25	Have you had attention problems?	96	1.4 (0.7)	67	26	6	2
26	Have you felt restless or agitated?	96	1.4 (0.7)	69	22	8	1
27	Have you felt hyperactive?*	96	1.2 (0.5)	85	10	5	0
28	Have you felt anxious?	96	1.2 (0.5)	79	18	3	0
29	Have you felt depressive?*	96	1.3 (0.6)	81	13	4	1
30	To what extent were you interested in sex?	87	1.8 (0.7)	37	47	15	2

1= Not at all

2= A little

3= Quite a bit

4= Very much

*Items 6,13,14,19,27 and 29 were deleted due to floor effects

The suitability of the data (remaining 24 items) for factor analysis was tested via the Kaiser-Meyer-Olkin (KMO) measure of sampling adequacy, which tests the partial correlations among the items. The KMO value should be higher than 0.5 for a satisfactory analysis to proceed ²¹. The KMO measure in this study was 0.84. Items with initial communalities < 0.10 should be deleted for further analyses; none of the items were deleted based on this criterion. Based on Cattell's scree plot and the Kaiser-Guttman rule (which states that an eigenvalue (the amount of the total variance explained by that factor) must be greater than one) 7 factors were identified. Oblique rotation, which assumes that the factors could be correlated with each other, simplified their interpretation by minimizing the items with high loadings on each factor. The seven factors cumulatively accounted for 46% of variation in all items (respectively 25%, 6%, 4%, 4%, 3%, 2%, 2%). Oblique rotation generates a pattern matrix with factor loadings and a structure matrix with correlations between items and components in a structure matrix (Table 3). A cut-off point of 0.35 for factor loadings was adopted, i.e. only those items scoring higher than this threshold were retained for further analyses. Six items were dropped based on this criterion and were treated as single items. The multi-trait scaling analysis showed that scaling assumptions were adequately met for four of the seven scales (Table 4). Cronbach's alpha coefficients range from 0.45-0.82, four of the seven scales scored higher than the preferred 0.70 level. Most scales of the thyroid specific questionnaire were weakly correlated ($r < 0.40$) with the QLQ-C30 (Table 5).

The resulting questionnaire, consisting of 24 items, was named THYCA-QoL (Attachment).

DISCUSSION

The THYCA-QoL has been methodologically developed using standard guidelines ¹⁵⁻¹⁷. It is designed for use in combination with the EORTC QLQ-C30 core instrument to assess all major dimensions of HRQoL in thyroid cancer survivors. The content of the questionnaire has been determined by an extensive literature search, and by interviews with HCP and thyroid cancer survivors. The next step of development (phase IV) involves administration in a large international group of thyroid cancer survivors to provide additional psychometric properties of the questionnaire.

Content validity was addressed in phase I to enlarge confidence that the instrument measures the aspects it was designed for. The content of our items is in agreement with the items of the non-validated Thyroid Cancer City of Hope Questionnaire (TCCHQ) ¹⁰⁻¹², however our questionnaire covers the whole spectrum of health problems thyroid cancer survivors' are dealing with. The TCCHQ adds four thyroid cancer specific questions to a more general HRQoL questionnaire, while our questionnaire adds 24 relevant items to the EORTC QOL-C30. Also,

scoring of the TCCHQ produces four general subscale scores (physical, psychological, social, spiritual), giving little specific information of how HRQoL is affected by thyroid cancer and its treatment. Because thyroid cancer survivors were extensively involved in the development of the questionnaire, our questions are more adapted to the terminology used by thyroid cancer survivors. Furthermore, the initial validation of the Thyroid Cancer Module of the M. D. Anderson Symptom Inventory is based on a small sample (n=60) of survivors who were not very symptomatic and were not representative for thyroid cancer survivors in general ¹³.

Table 3: Rotated component matrix (factor loadings)

Item	Description	Pattern matrix							Structure matrix						
		1	2	3	4	5	6	7	1	2	3	4	5	6	7
First factor: Neuromuscular															
15	Cramps legs	0.523							0.600						
16	Felt slowed down (physically)	0.514							0.570						
11	Pain muscles/joints	0.360							0.513						
Second factor: Voice															
3	Hoarseness		0.860							0.854					
4	Weak voice		0.716							0.724					
Third factor: Concentration															
25	Attentional problems			-0.852							-0.853				
24	Difficulty thinking			-0.588							-0.731				
Fourth factor: Sympathetic															
10	Hot flushes				0.832							0.862			
9	Sensitive heat				0.541							0.664			
Fifth factor: Throat/mouth															
2	Problems swallowing					0.808							0.820		
5	Lump in throat					0.414							0.534		
1	Dry mouth					0.400							0.478		
Sixth factor: Psychological															
28	Anxious						0.602							0.552	
26	Restless						0.572							0.713	
21	Palpitations						0.498							0.600	
23	Abrupt tiredness						0.360							0.627	
Seventh factor: Sensory															
18	Eye problems							0.548							0.601
20	Skin problems							0.528							0.514

Items 7 (scar), 8 (chilly), 12 (tingling hands/feet), 17 (gained weight), 22 (headaches), 30 (interested in sex) were not included in a factor and were therefore seen as single items.

Table 4: Summary of results of multi-trait scaling

Scale	N	Mean (SD)	Cronbach's alpha	Item-scale convergent validity Criterion 1 (inclusive criterion)		Item-scale divergent validity Criterion 2 (exclusive criterion)		Scaling fulfillment
				Range of item-scale correlations ¹	Number of item-scale correlations ²	Range of correlations with other scales ³	Number of items higher correlations with other scale ⁴	
1 Neuromuscular (15 cramp legs; 16 felt slowed down (physically); 11 pain joints/muscles)	3	24.1 (21.9)	0.63	0.428-0.486	3/3	0.108-0.539	1/3	2/3
2 Voice (3 hoarseness; 4 weak voice)	2	11.0 (18.9)	0.76	0.620	2/2	0.086-0.382	0/2	2/2
3 Concentration (25 attentional problems; 24 difficulty thinking)	2	15.9 (21.8)	0.82	0.695	2/2	0.143-0.625	0/2	2/2
4 Sympathetic (10 hot flushes; 9 sensitive heat)	2	18.7 (25.5)	0.76	0.620	2/2	0.182-0.516	0/2	2/2
5 Throat/mouth problems (2 problems swallowing; 5 lump in throat; 1 dry mouth)	3	12.9 (17.1)	0.62	0.340-0.581	1/3	0.108-0.442	2/3	1/3
6 Psychological (28 anxious; 26 restless; 21 palpitations; 23 abrupt tiredness)	4	14.4 (16.6)	0.72	0.423-0.617	4/4	0.083-0.570	0/4	4/4
7 Sensory (18 eye problems; 20 skin problems)	2	15.1 (19.7)	0.45	0.288	0/2	0.114-0.357	1/2	1/2

1. Pearson correlation between items and hypothesized scale (corrected for overlap).
2. Number of item-scale correlations that meet minimum standard for convergent validity (≥ 0.40).
3. Pearson correlations between items and other scales.
4. Correlations higher between items and other scales in comparison with hypothesized scale

Some limitations of the module development should be acknowledged. First, the results confirmed the hypothesized scale structure and reliability of 4 of 7 of the multi-item scales (voice, concentration, sympathetic and psychological problems), with reliability estimates between 0.72 and 0.82. In contrast, the reliability of the neuromuscular, throat/mouth and sensory problem scales was suboptimal (0.63, 0.62 and 0.45, respectively). The lower reliability observed for these scales may reflect the limited variability observed in the scores of the items comprising these scales. The lower reliability estimates will not necessarily negate the value of the scales, since survivors and HCP rated the items as relevant during phase I of the development process. Given that the found scales were in line with the expectations we had after reviewing the literature and a scale structure could improve clinical interpretability, we preferred to keep the scale structure rather than treating those items as single ones. Since we also used the same patient sample for the factor analysis as well as for the multi-trait analysis, our hypothesized scale structure must be further confirmed in another large (international) sample of diverse thyroid cancer survivors. Statistical techniques from the Item Response Theory (IRT) will be used for the final validation of the questionnaire and its hypothesized scales.

Second, during phase III, the provisional module was tested in a group of 306 survivors of which almost half (45%) was diagnosed more than 10 years ago, creating a potential for bias (floor/ceiling effects). Results from the focus group indicated that the kind of problems thyroid cancer survivors are dealing with do not differ across the cancer continuum, only the severity of the problems changes over time. In the next phase of questionnaire development, the method of known-groups validation must be used to assess the ability of the THYCA-QoL to distinguish between subgroups of thyroid cancer survivors with regard to years since diagnosis, disease stage, treatment, and histology. The study sample of the next development phase should include more medullary thyroid cancer patients, since the number of those patients was too low in the provisional test phase to test the applicability of the questionnaire within this group. Also, as is recommended by the EORTC, the responsiveness to change and the cross-cultural validity need to be tested in the last phase of questionnaire development¹⁵⁻¹⁷.

The THYCA-QoL is the first thyroid cancer specific HRQoL questionnaire developed using standard methodologically proven guidelines. This questionnaire can be of value in the treatment and after care of thyroid cancer survivors. It will make medical doctors more aware of the potential HRQoL issues thyroid cancer survivors are dealing with. Also, this questionnaire helps doctors to provide survivors with adequate information on HRQoL and thereby improve survivors' experiences of their illness. After the phase IV validation is completed, the questionnaire can be used in future trials of new and existing treatments for thyroid cancer survivors. It may also be of value in the longitudinal follow-up of survivors in order to find survivors who are most vulnerable for health problems and to arrange additional help for those who need it.

Table 5: Correlations between EORTC QLQ-C30 and scales/items THYCA-QoL

EORTC QLQ-C30	Factor 1 Neuromuscular	Factor 2 Voice	Factor 3 Concentration	Factor 4 Sympathetic	Factor 5 Throat/mouth	Factor 6 Psychological	Factor 7 Sensory	SC	CH	THF	GW	HA	SXI
Physical functioning	-0.62**	-0.17**	-0.33**	-0.38**	-0.34**	-0.50**	-0.21**	-0.18**	-0.29**	-0.34**	-0.05	-0.26**	0.31**
Role functioning	-0.60**	-0.13*	-0.39**	-0.39**	-0.30**	-0.47**	-0.22**	-0.22**	-0.23**	-0.38**	-0.06	-0.30**	0.18**
Emotional functioning	-0.48**	-0.16**	-0.47**	-0.38**	-0.34**	-0.65**	-0.24**	-0.19**	-0.30**	-0.33**	-0.18**	-0.34**	0.03
Cognitive functioning	-0.43**	-0.14*	-0.76**	-0.37**	-0.32**	-0.51**	-0.16**	-0.23**	-0.34**	-0.38**	-0.17**	-0.26**	0.06
Social functioning	-0.56**	-0.22**	-0.54**	-0.42**	-0.32**	-0.57**	-0.24**	-0.20**	-0.28**	-0.38**	-0.20**	-0.28**	0.11
Global QoL/health status	-0.56**	-0.20**	-0.43**	-0.42**	-0.33**	-0.55**	-0.26**	-0.19**	-0.26**	-0.31**	-0.16**	-0.38**	0.19**
Fatigue	0.65**	0.26**	0.51**	0.50**	0.41**	0.72**	0.27**	0.26**	0.35**	0.42**	0.18**	0.48**	-0.15
Nausea/vomiting	0.29**	0.16**	0.28**	0.18**	0.37**	0.35**	0.15**	0.15*	0.24**	0.28**	0.12*	0.27**	-0.10
Pain	0.61**	0.11	0.29**	0.34**	0.28**	0.43**	0.25**	0.19**	0.19**	0.28**	-0.01	0.33**	-0.15*
Dyspnoea	0.41**	0.06	0.32**	0.32**	0.24**	0.44**	0.19**	0.20**	0.31**	0.24**	0.01	0.22**	-0.20**
Sleep/insomnia	0.38**	0.16**	0.31**	0.37**	0.25**	0.46**	0.18**	0.21**	0.15*	0.25**	0.01	0.35**	-0.11
Appetite loss	0.35**	0.33**	0.24**	0.15**	0.48**	0.34**	0.13*	0.11	0.32**	0.23**	-0.02	0.27**	-0.10
Constipation	0.29**	0.07	0.14*	0.26**	0.29**	0.19**	0.18**	0.05	0.10	0.16**	0.09	0.16**	-0.13*
Diarrhoea	0.19**	0.15**	0.16**	0.25**	0.28**	0.25**	0.10	0.10	0.11	0.22**	-0.01	0.13*	0.03
Financial difficulties	0.38**	0.09	0.28**	0.26**	0.19**	0.28**	0.13*	0.22**	0.18**	0.22**	0.13**	0.22**	0.05

<0.40 = Weak correlation, 0.40-0.60 = moderate and >0.60 = high

*p<0.05; ** p<0.01

SC = Did the scar in your neck bothered you; CH = Have you felt chilly; THF = Did you have tingling hands and/or feet; GW = Have you gained weight ; HA = Did you have headaches ; SXI = To what extent were you interested in sex

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Attachment: Final 24 items of the THYCA-QoL questionnaire

1. Have you had a dry mouth?
2. Have you had trouble swallowing?
3. Have you been hoarse?
4. Have you had a weak voice?
5. Have you had a lump in your throat?
6. Did the scar in your neck bother you?
7. Have you felt chilly?
8. Have you had difficulty tolerating heat?
9. Have you had hot flushes?
10. Have you had pain in your muscles and/or joints?
11. Have you had tingling hands and/or feet?
12. Have you had cramps in your legs?
13. Have you felt slowed down?
14. Have you gained weight?
15. Have you had painful, irritated or dry eyes?
16. Have you had skin problems (e.g. itchy, dry)?
17. Have you suffered from palpitations?
18. Have you had headaches?
19. Have you had abrupt attacks from tiredness?
20. Have you had troubles with thinking?
21. Have you had attention problems?
22. Have you felt restless or agitated?
23. Have you felt anxious?
24. To what extent were you interested in sex?

CHAPTER 11

Health-related quality of life and disease specific symptoms in long-term thyroid cancer survivors: a study from the population-based PROFILES registry

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ABSTRACT

Background: Given the longevity of thyroid cancer patients, any impairment in health-related quality of life (HRQoL) during the follow-up period is of considerable concern. Therefore, the first aim of this study was to assess (thyroid cancer specific) HRQoL among long-term thyroid cancer survivors and to compare this with the HRQoL of an age- and sex-matched normative population. Secondly, our aim was to investigate which clinical and socio-demographic characteristics and thyroid cancer specific problems were associated with HRQoL.

Material and methods: All patients diagnosed with thyroid cancer between 1990-2008, as registered in the Eindhoven Cancer Registry, received a survey on HRQoL (EORTC QLQ-C30) and disease-specific symptoms (THYCA-QoL). The scores were compared with age-and-sex-matched cancer free controls (n=800). A series of multiple linear regression analyses were conducted to investigate the independent associations between clinical, socio-demographic and thyroid cancer specific factors with HRQoL.

Results: A total of 306 patients (86%) responded to the invitation. Thyroid cancer survivors had significantly lower scores on physical, role, emotional, cognitive and social functioning ($p<0.001$) compared to the normative population after adjusting for comorbidities. Sympathetic problems (feeling chilly (52%), hot flushes (40%)), neuromuscular problems (cramp legs (43%) and pain joints/muscles (64%)) and abrupt attacks of fatigue (50%) were the most often reported thyroid cancer specific complaints.

Thyroid cancer specific neuromuscular, concentration, sympathetic and psychological problems explained 41-58% of the variance in HRQoL. Clinical and socio-demographic factors explained a small part of the variance in (thyroid cancer specific) HRQoL (1-27%).

Conclusion: Thyroid cancer survivors experience symptoms and deteriorated HRQoL long after diagnosis. Thyroid cancer specific neuromuscular, sympathetic, concentration and psychological symptoms are stronger associated with HRQoL than clinical and socio-demographic factors alone. Awareness of these specific determinants of HRQoL could help health care practitioners to provide better supportive care.

INTRODUCTION

In the Netherlands, the incidence of thyroid cancer (TC) is 3.1 cases per 100.000 people per year. Each year 570 patients are diagnosed with TC ¹. Worldwide incidence rates are rising ². The incidence is 2.5 times higher in women than in men. The papillary and follicular type account for about 80-90% of all cases, and poorly differentiated (medullary and anaplastic) TCs for about 10-20%. As a result of the very good prognosis of papillary or follicular TC (exceeding >90% 5-year survival rates) the number of TC survivors is growing ³.

Treatment of TC involves surgery, predominantly (near-)total thyroidectomy with or without lymphadenectomy, followed by radioiodine (iodine-131) therapy to ablate the remaining thyroid tissue. Depending on type and size of the tumour hemithyroidectomy could suffice. The removal of the whole thyroid gland is accompanied by a lifelong dependence on supplement therapy with thyroid hormone (levothyroxine), in the first years with dosing regimes suppressing thyroid stimulating hormone (TSH) production ⁴. Despite the efficacy of these primary treatments and the high long-term survival rates, 15-35% of the patients develop a locoregional recurrence or distant metastases, even decades later ⁵. Therefore, intensive long-term periodical follow-up is necessary.

Given the longevity of TC patients, possible impairments in health-related quality of life (HRQoL) during the follow-up period are of considerable concern. There is a limited number of studies focusing on HRQoL among TC survivors that moreover show contradictory results ⁶. A few studies found a lower HRQoL for TC survivors compared with a reference group, whereas other studies found similar HRQoL levels ⁶. The main problem of previous studies is the lack of a valid, specific instrument to assess the HRQoL among TC survivors. Therefore, we recently developed a TC specific HRQoL questionnaire to unveil specific TC related complaints ⁷. Furthermore, most other studies were inconclusive because they had small sample sizes and focused on short-term TC survivors (<2 years after diagnosis) ⁶. Consequently little is known about long-term HRQoL in TC patients. Therefore, the primary objective of our study was to assess general and TC specific HRQoL of long-term TC survivors and to compare this with an age- and sex-matched normative population. To be able to tailor supportive care to the individual needs of TC patients, it is important to obtain insight into the factors influencing HRQoL. Therefore our second aim was to investigate which clinical and socio-demographic characteristics and TC specific problems were associated with HRQoL.

METHODS

Setting and population

This study is a population-based survey among TC survivors registered within the Eindhoven Cancer Registry (ECR) of the Comprehensive Cancer Centre South (CCCS). The ECR compiles data of all individuals newly diagnosed with cancer in the southern part of the Netherlands, an area with 10 hospitals serving 2.3 million inhabitants ⁸. All individuals diagnosed with TC between 1990-2008 as registered in the ECR were eligible for participation (N=568) (Figure 1). We excluded patients who had cognitive impairment or were too ill at time of the study (N=31), had unverifiable addresses (N=90), or died prior to the start of the study (according to the ECR, hospital records, and the Central Bureau for Genealogy (N=6). One hospital declined to participate (N=86). The study was approved by the Medical Ethics Committee of the Maxima Medical Centre Eindhoven.

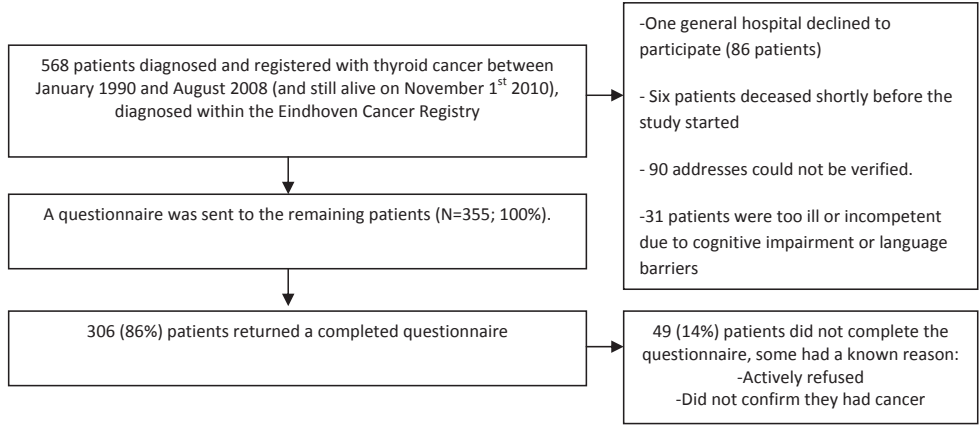


Figure 1: Flow-chart of the data collection process

Data collection

Data collection was conducted in November 2010 within PROFILES (Patient Reported Outcomes Following Initial treatment and Long term Evaluation of Survivorship). PROFILES is a registry for the study of the physical and psychosocial impact of cancer and its treatment from a dynamic, growing population-based cohort of both short and long-term cancer survivors. PROFILES contains a large web-based component and is linked directly to clinical data from the ECR. Survivors were informed about the survey via a letter from their (ex)-attending specialist. The letter explained that by completing the questionnaire (online or by pencil-and-paper), patients consented to participate and agreed to the linkage of the questionnaire data with their disease history in the ECR. Further details of the data

collection method have been described previously ⁹. Data from the PROFILES registry will be available for non-commercial scientific research, subject to study question, privacy and confidentiality restrictions, and registration (www.profilesregistry.nl).

Study measures

Socio-demographic and clinical characteristics

Clinical information of the survivors was available from the ECR. The ECR routinely collects data on tumour characteristics, including date of diagnosis, disease stage, primary treatment, and patient background characteristics including date of birth.

Questions on marital status, educational level, and current occupation were added to the questionnaire. Comorbidity at the time of survey was categorized according to an adapted Self-administered Comorbidity Questionnaire (SCQ) ¹⁰, including heart disease, stroke, high blood pressure, long disease, diabetes, ulcer or stomach disease, kidney disease, anemia or other blood disease, depression, osteoarthritis, back pain, rheumatoid arthritis and a question on other medical problems.

EORTC-QLQ-C30

HRQoL was measured by the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC-QLQ-C30) ¹¹. This 30-item HRQoL questionnaire consists of five functional scales (physical, role, cognitive, emotional and social), a global quality of life scale, 3 symptom scales (fatigue, pain, nausea and vomiting) and a number of single items assessing common symptoms (dyspnoea, loss of appetite, sleep disturbance, constipation and diarrhea) and perceived financial impact of the disease. The time frame of the questions is the previous week, and each item is scored on a 4 point response scale ranging from 1, 'not at all' to 4, 'very much,' with the exception of the global QoL scale, which is scored on a 7-point modified linear analogue scale ranging from 1, 'very poor' to 7, 'excellent'. After linear transformation, all scales and single item measures range in score from 0-100. A higher score on the functional scales and global QoL means better functioning and HRQoL, whereas a higher score on the symptom scales means more complaints.

Thyroid cancer specific HRQoL (THYCA-QoL)

TC specific HRQoL was measured by a self-developed questionnaire (THYCA-QoL) to assess side-effects due to TC or its treatment ⁷. We developed and validated the TC specific HRQoL questionnaire according to the methods of the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life group. The questionnaire consists of 24 items, with a time frame of the previous week (except for the sexual interest item which is four weeks) and each item is scored on a 4 point response scale ranging from 1, 'not at all' to 4, 'very much'. The THYCA-QoL consists of seven symptom scales (neuromuscular, voice,

concentration, sympathetic, throat/mouth, psychological and sensory problems) and six single items (problems with scar, felt chilly, tingling hands/feet, gained weight, headaches, interest in sex). Scores were linear transformed to a 0-100 scale. A higher score on this scale means more symptoms.

Normative population

Normative population data was obtained from CentERpanel, an online household panel that is representative of the Dutch population. The process of the annual data collection, which started in 2009 by our study group, is described elsewhere¹². The data wave in 2009 included assessment of HRQoL (EORTC QLQ-C30). From the 1731 members ≥ 18 years who responded (78%), an age-and-sex-matched normative cancer-free sample ($n=800$) was selected for this study to reflect the age and sex distribution of the TC sample. Socio-demographic data were also collected for this group.

Statistical analyses

Differences in clinical and socio-demographic characteristics between respondents, non-respondents and patients with unverifiable addresses and between TC patients and the normative population were compared using chi-square statistics for categorical variables and t-tests or analysis of variance (ANOVA) for continuous variables.

ANCOVA was used to compare the mean scores on the individual EORTC QLQ-C30 scales between TC survivors and the normative population, controlled for the number of comorbidities. In addition, clinical meaningfulness of the differences was determined according to the guidelines of the EORTC Quality of Life Group¹³. Differences in (TC specific) HRQoL between subgroups of survivors (<5 years; 5-10 years; > 10 years since diagnosis) were analyzed using ANOVA.

A series of multiple linear regression analyses (enter method) were conducted to investigate the independent associations between clinical (disease stage, primary treatment, comorbidity) and socio-demographic characteristics (age, sex, partner, educational level) with subscale scores of the EORTC-QLQ-C30 and THYCA-QoL. Also, independent associations of the TC specific problems with the subscales of the EORTC QLQ-C30 were analyzed with multiple linear regression analyses and were adjusted for clinical and socio-demographic variables (determined a priori).

All statistical analyses were performed using SPSS version 17.0 (Statistical Package for Social Sciences, Chicago, IL, USA) and P values $< .05$ were considered statistically significant.

RESULTS

Patient and tumour characteristics

Three hundred and six patients returned a completed questionnaire (response 86%). A comparison between respondents, non-respondents and patients with unverifiable addresses indicated that patients with unverifiable addresses were younger compared to non-respondents and respondents. No differences between groups were seen regarding sex, type of TC, stage of the disease or primary treatment.

The mean age at diagnosis was 46 (SD=15) years (Table 1). Average time since diagnoses was 9.6 (SD= 5.5) years. More than half of the patients were diagnosed with stage I disease (57%). Surgery (99%) was followed by iodine-131 ablation therapy in 69% and by radiotherapy in 3% of the cases. More than three quarters (78%) of the patients had one or more comorbid conditions. The most common comorbidities were backache (36%), high blood pressure (29%), arthrosis (28%) and cardiovascular problems (12%).

TC patients reported more often the presence of comorbid conditions and more often had a lower educational level compared to the normative population (Table 1). No differences between groups were seen in age, sex, partnership and occupation.

HRQoL of TC survivors compared with normative population

HRQoL of TC survivors as measured by the EORTC-QLQ-C30 was compared with an age- and-sex-matched normative sample from the general Dutch population (Figure 2a/2b). The survivors had significantly lower scores on physical (83 vs. 89), role (82 vs. 88), emotional (83 vs. 88), cognitive (82 vs. 92) and social functioning (85 vs. 93; all $p < 0.001$) compared to the normative population after adjusting for comorbidities. No differences were seen in global health. According to the guidelines of the EORTC Quality of Life Group, the differences between TC survivors and normative population were of small clinical importance for the subscales physical, role and social functioning and medium for cognitive functioning. The clinical importance of the difference for the emotional functioning scale could not be determined¹³.

TC survivors had significantly more symptoms of fatigue (28 vs. 18), dyspnoea (14 vs. 8), insomnia (22 vs. 16), appetite (6 vs. 4), constipation (10 vs. 6; all $p < 0.001$), diarrhea (7 vs. 4; $p < 0.01$) and had higher scores on financial difficulties (10 vs. 3; $p < 0.001$) compared to the normative population after adjusting for comorbidities. No differences were seen for nausea and pain. The differences were of small clinical importance for fatigue, dyspnoea, insomnia and financial difficulties and of no clinical importance for appetite, constipation and diarrhea.

Table 1: Clinical and socio-demographic characteristics of questionnaire of respondents and the normative population

	N (%)		P-value
	Respondents (N= 306)	Normative population (N=800)	
Age at time survey in years (mean (\pmSD))	56.4 (14.5)	55.1 (13.5)	0.15
Years since diagnosis	9.6 (5.5)	-	-
25 th percentile	4.7	-	
Median	9.0	-	
75 th percentile	13.5	-	
Sex			0.95
Male	76 (24.8%)	200 (25.0%)	
Female	230 (75.2%)	600 (75.0%)	
Type of thyroid cancer			-
Papillar	217 (70.9%)	-	
Follicular (including Hurthle cell)	73 (23.8%)	-	
Medullary	13 (4.2%)	-	
Stage			-
I	172 (57.1%)	-	
II	59 (19.6%)	-	
III	48 (15.9%)	-	
IV	20 (6.6%)	-	
Primary treatment			-
Surgery	83 (27.1%)	-	
Surgery + iodine-131 ablation	212 (69.3%)	-	
Surgery + radiotherapy	9 (2.9%)	-	
Other	2 (0.7%)	-	
Comorbidity (self-report)			<0.001
None	68 (22.2%)	319 (39.9%)	
1	70 (22.9%)	208 (26.0%)	
≥ 2	168 (54.9%)	273 (34.1%)	
Partnership			0.48
Partner	238 (77.8%)	606 (75.8%)	
No partner	68 (22.2%)	194 (24.3%)	
Educational level			0.01
High	80 (26.2%)	261 (32.7%)	
Middle	192 (63.0%)	491 (61.6%)	
Low	33 (10.8%)	45 (5.6%)	
Current occupation			0.20
Employed	154 (51.3%)	376 (47.0%)	
Not employed	146 (48.7%)	424 (53.0%)	

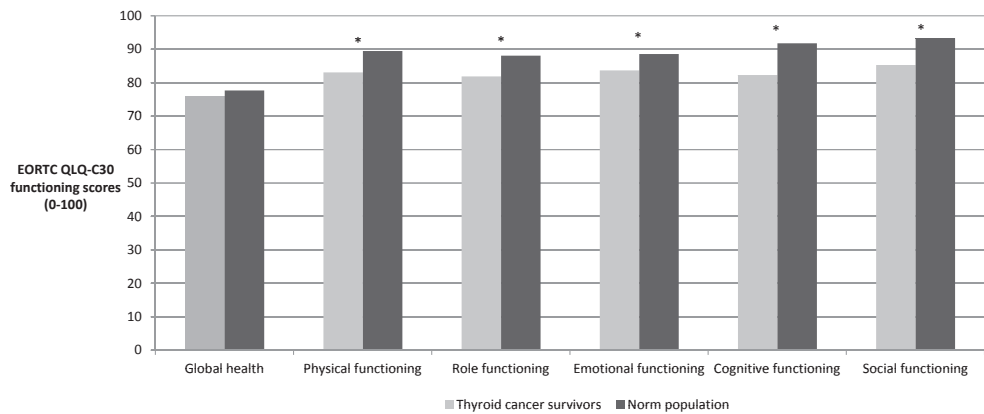


Figure 2a: HRQoL of thyroid cancer survivors compared to normative population

Mean EORTC-QLQ-C30 functioning subscale scores (0-100) of survivors in comparison with a Dutch normative population. A higher scores means better functioning. An asterisk above the bar indicates a group difference (ANCOVA, $p < 0.05$, adjusted for comorbidity).

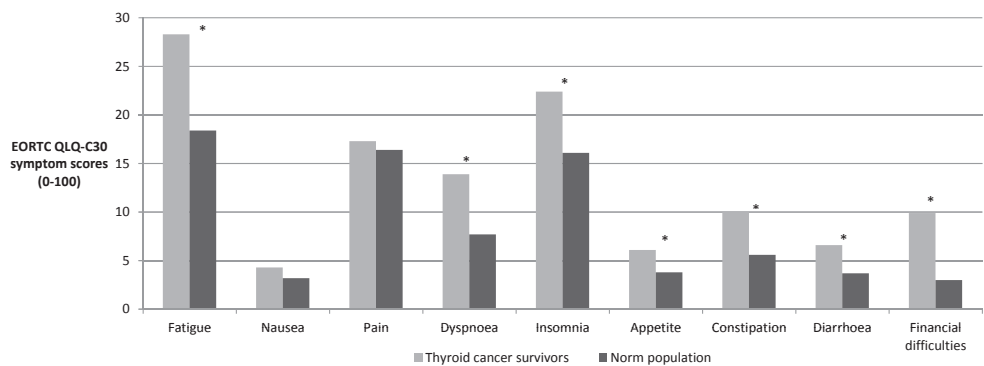


Figure 2b: HRQoL of thyroid cancer survivors compared to normative population

Mean EORTC-QLQ-C30 symptom subscale scores (0-100) of survivors in comparison with a Dutch normative population. A higher score indicates more symptoms. An asterisk above the bars indicates a group difference (ANCOVA, $p < 0.05$, adjusted for comorbidity).

Thyroid cancer specific HRQoL

The majority of TC survivors experienced disease specific symptoms during the past week. Sympathetic problems (feeling chilly (52%), hot flushes (40%)), neuromuscular problems (cramp legs (43%) and pain joints/muscles (64%)) and abrupt attacks of fatigue (50%) were the most often reported complaints.

Table 2: Mean scores (\pm SD) of thyroid cancer survivors on EORTC QLQ-C30 and THYCA-QoL scales (0-100) and single items according to years since diagnosis.

	Survivors <5 years since diagnosis N = 81	Survivors 5-10 years since diagnosis N=86	Survivors >10 years since diagnosis N=137	P-value#
EORTC QLQ-30 functioning+				
Global health	73.8 (18.2)	74.4 (21.2)	77.6 (20.2)	0.3
Physical functioning	82.0 (19.7)	83.5 (19.7)	83.0 (19.5)	0.9
Role functioning	79.8 (26.8)	84.3 (24.6)	81.1 (28.3)	0.5
Emotional functioning	83.6 (16.3)	81.1 (22.8)	84.9 (20.2)	0.4
Cognitive functioning	80.4 (20.4)	79.5 (27.3)	84.7 (20.1)	0.2
Social functioning	85.8 (22.1)	82.1 (29.7)	86.6 (22.9)	0.4
EORTC QLQ-30 symptoms++				
Fatigue	30.9 (24.6)	29.0 (28.3)	26.0 (23.8)	0.4
Nausea	4.3 (11.1)	5.8 (14.1)	3.1 (8.4)	0.2
Pain	17.5 (25.4)	17.5 (25.9)	16.8 (24.1)	0.9
Dyspnoea	14.8 (21.7)	14.9 (22.8)	12.7 (22.2)	0.7
Insomnia	27.2 (29.9)	21.3 (29.7)	20.1 (28.5)	0.2
Appetite	9.1 (21.7)	6.3 (20.4)	3.9 (13.4)	0.1
Constipation	11.9 (21.9)	8.7 (18.0)	9.5 (19.8)	0.6
Diarrhea	7.0 (18.0)	7.9 (20.4)	5.4 (14.2)	0.5
Financial difficulties	10.3 (19.5)	11.5 (26.1)	8.4 (20.7)	0.6
THYCA-QoLscales ++				
Neuromuscular	27.7 (22.1)	23.8 (23.3)	22.1 (20.7)	0.2
Voice	16.0 (22.7)	12.1 (20.6)	7.3 (14.1)	0.01
Concentration	19.6 (21.5)	18.5 (25.2)	12.1 (18.9)	0.02
Sympathetic	23.3 (29.2)	21.8 (28.3)	14.0 (20.1)	0.02
Throat/mouth	19.3 (20.1)	13.2 (18.1)	8.9 (13.1)	<0.01
Psychological	16.9 (17.1)	15.8 (18.7)	11.9 (14.6)	0.07
Sensory	17.5 (19.2)	14.3 (19.8)	14.2 (19.9)	0.5
THYCA-QoLsingle items ++				
Problems with scar	16.5 (26.9)	9.1 (23.3)	8.0 (20.1)	0.03
Felt chilly	31.7 (32.9)	26.8 (31.6)	23.4 (30.6)	0.2
Tingling hands/feet	17.7 (27.4)	17.9 (25.1)	11.6 (24.0)	0.1
Gained weight	12.2 (18.6)	12.9 (20.6)	9.4 (17.7)	0.3
Headaches	18.8 (24.8)	19.8 (26.4)	16.4 (23.5)	0.6
Less interest in sex+	24.2 (23.3)	35.6 (25.8)	24.4 (24.4)	<0.01

+ Higher scores indicate better functioning; ++ Higher scores indicate more symptoms

P-value of ANOVA for differences between the three groups (results of post-hoc tests are described in text)

Clinical and socio-demographic factors associated with (thyroid cancer specific) HRQoL

When stratified by years since diagnosis (<5 years; 5-10 years; > 10years since diagnosis) no differences between the groups were seen in functioning and symptom scales of the EORTC QLQ-C30. TC survivors >10 years since diagnosis reported less TC specific voice, concentration, sympathetic, throat/mouth problems compared to survivors <5 years since diagnosis (Table 2). Survivors < 5 years since diagnosis reported more problems with their scar compared to survivors 5-10 years and >10 years since diagnosis.

Table 3: Standardized betas of multivariate linear regression analyses evaluating the association of independent variables with the HRQoL scales.

	EORTC QLQ-C30 – scales+					
	Global health	Physical functioning	Role functioning	Emotional functioning	Cognitive functioning	Social functioning
Age	-0.01	-0.21 **	-0.05	0.19**	0.06	0.11
Years since dx	0.09	0.01	-0.02	-0.02	0.10	-0.03
Sex	0.07	-0.03	0.02	0.07	0.10	0.06
Type of cancer						
Papillar	Ref	Ref	Ref	Ref	Ref	Ref
Follicular	-0.05	-0.07	-0.01	0.01	0.04	-0.01
Medullary	-0.05	-0.09	-0.07	0.03	-0.02	-0.01
Primary treatment	-0.06	-0.01	0.01	0.02	-0.11	-0.05
Stage	-0.01	-0.05	-0.05	-0.19**	-0.02	-0.08
Comorbidity	-0.24**	-0.24 **	-0.17**	-0.18**	-0.06	-0.07
Partner	-0.21**	-0.24**	-0.21**	-0.12	-0.13*	-0.23**
Education	-0.13*	-0.14*	-0.17**	-0.06	-0.14*	-0.12
R²	0.14	0.27	0.14	0.08	0.06	0.08

*<0.05; **<0.01

+ Higher score indicates better functioning

Abbreviations: dx = diagnosis

Age and Years since dx were continuous variables in the multivariate model.

Other variables were sex: male vs. female; type of cancer: papillar vs. follicular and papillar vs. medullary; primary treatment: surgery vs. surgery + ablation; disease stage: stage I/II vs. stage III/IV; comorbidity: no comorbid conditions vs. one or more comorbid conditions; partner: partner vs. no partner; educational level: high vs. low.

Multivariate linear regression analyses showed that clinical factors (type of cancer, primary treatment, stage of disease, years since diagnosis) were not associated with the functional and symptom scales of the EORTC QLQ-C30, except for disease stage which was negatively associated with emotional functioning (Table 3). Having one or more comorbidities was associated with worse global health and physical, role and emotional functioning and more fatigue (Beta = 0.24; p<0.05), pain (Beta = 0.25; p<0.05), dyspnoea (Beta = 0.18; p<0.05), insomnia (Beta = 0.17; p<0.05) and less appetite (Beta = 0.15; p<0.05). Higher age was

associated with worse physical functioning and better emotional functioning. Absence of a partner and lower educational level were associated with worse functioning (Table 3) and more symptoms (Betas ranging from 0.12 – 0.24; $p < 0.05$).

Most clinical variables were not associated with TC specific problems (neuromuscular, psychological and sensory problems; feeling chilly, tingling hands/feet, gaining weight, headaches, interest in sex; Table 4). However fewer years since diagnosis was associated with more voice, throat and scar problems (Beta = -0.14; $p < 0.05$). Medullar TC and a higher stage disease were associated with more sympathetic problems. More comorbidities, absence of a partner and lower educational level were associated with more TC specific symptoms (Table 4). The explained variance (R^2) of clinical and socio-demographic variables ranged from 1% to 27%.

Table 4: Standardized betas of multivariate linear regression analyses evaluating the association of independent variables with the thyroid cancer specific symptom scales.

	THY-QoL - scales+						
	Neuro-muscular	voice	concentration	Sympathetic	Throat/mouth	Psychological	Sensory
Age	0.08	0.12	-0.19**	-0.01	0.05	-0.11	-0.02
Years since dx	-0.07	-0.17**	-0.08	-0.11	-0.23**	-0.10	-0.05
Sex	-0.01	0.09	-0.11	0.16**	0.02	0.04	-0.02
Type of cancer							
Papillar	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Follicular	-0.05	-0.01	-0.07	0.04	0.02	0.02	0.09
Medullar	0.01	0.02	0.01	0.13*	-0.02	-0.06	0.07
Primary treatment	0.10	0.02	0.10	0.07	-0.05	0.06	0.06
Stage	0.05	0.16*	0.13	0.15*	0.16*	0.10	-0.01
Comorbidity	0.26**	-0.02	0.09	0.09	0.17**	0.20**	0.20**
Partner	0.14*	-0.04	0.18**	0.09	-0.03	0.16**	0.01
Education	0.20**	0.03	0.17**	0.06	0.10	0.09	0.05
R²	0.19	0.10	0.11	0.11	0.15	0.11	0.06

* < 0.05 ; ** < 0.01

+ Higher score is more symptoms

Abbreviations: dx = diagnosis

Age and Years since dx were continuous variables in the multivariate model.

Other variables were sex: male vs. female; type of cancer: papillar vs. follicular and papillar vs. medullary; primary treatment: surgery vs. surgery + ablation; disease stage: stage I/II vs. stage III/IV; comorbidity: no comorbid conditions vs. one or more comorbid conditions; partner: partner vs. no partner; educational level: high vs. low.

Multivariate linear regression analyses, corrected for socio-demographic and clinical characteristics showed that more neuromuscular problems were associated with worse global health (Beta = -0.23; $p < 0.05$), physical (Beta = -0.35; $p < 0.01$), role (Beta = -0.31; $p < 0.01$), emotional (Beta = -0.16; $p < 0.05$) and social functioning (Beta = -0.36; $p < 0.01$).

More concentration problems were associated with worse cognitive (Beta = -0.73; $p < 0.01$) and social functioning (Beta = -0.23; $p < 0.01$), while more sympathetic problems were associated worse global health (Beta = -0.17; $p < 0.05$). More psychological problems were associated with worse physical (Beta = -0.25; $p < 0.05$), emotional (Beta = -0.53; $p < 0.01$) and social functioning (Beta = -0.22; $p < 0.01$) and worse global health (Beta = -0.19; $p < 0.05$). The explained variance (R^2) ranged from 41% for global health and 58% for cognitive functioning.

DISCUSSION

Our findings showed that TC survivors report statistically significant and clinically relevant lower levels of physical and psychosocial functioning, and significantly more symptoms compared to an age- and sex-matched normative population. TC-specific neuromuscular, concentration, sympathetic and psychological problems were most strongly associated with worse physical and psychosocial functioning.

Primary treatment was not associated with HRQoL, which is in agreement with an earlier study that found no differences in HRQoL scores between patients who underwent total thyroidectomy and hemithyroidectomy respectively¹⁴. A recent study showed that those patients submitted to higher doses of radioactive iodine are at risk for poor HRQoL¹⁵. For part of the patients there may be overtreatment, since low-risk patients are unlikely to benefit from radioactive iodine therapy after initial surgery¹⁶. Unfortunately, no data on doses of radioactive iodine were available in the present study. Furthermore, the recent use of recombinant human thyroid stimulating hormone (rhTSH) as alternative for thyroid hormone withdrawal preserved HRQoL during radioactive iodine ablation⁶.

Disease stage and time since diagnosis were not related to HRQoL, although high disease stage and short time since diagnosis were related to more TC-specific voice and throat/mouth problems, indicating the severity of surgery. Our results show that TC-specific problems related to thyroid dysregulation (neuromuscular, concentration, sympathetic, psychological and sensory problems) were most strongly associated with HRQoL. Although TC-specific symptoms diminish over time, they remain present long after initial treatment. The high doses of replacement therapy (TSH < 0.1 mU/L) in the first years of follow-up, for patients who underwent ablation therapy or had high risk of recurrence, and the subsequent TSH suppression may cause symptoms of subclinical hyperthyroidism. After the first years the doses of replacement therapy will be lowered for low-risk survivors (TSH level around median (1 mU/L)), however the lower doses might not be the optimal (pre-operative) level for the specific patient and in that case the symptoms are a result of the supplemental thyroid hormone treatment¹⁷. Furthermore, long-term exposure to excess thyroid hormone

can lead to (irreversible) changes of the autonomous nervous system, which could not be reversed by restoration to euthyroidism¹⁸. These changes possibly influence the well-being of a patient and might be an explanation for the symptoms patients experience even long-term after diagnosis.

Having one or more comorbidities was associated with worse functioning and more (TC specific) symptoms. Comorbid conditions could affect the presentation and recognition of symptoms and result in worse HRQoL on their own. Since 78% of the survivors reported one or more comorbidities, it is unclear whether comorbidity is associated with lower HRQoL or whether it is the disease itself, or their collaborative effect that negatively impacts HRQoL. Since the prevalence of comorbidities in the normative population (natural aging effects) was significantly lower compared to TC survivors, this might indicate that part of the comorbid diseases developed after primary treatment for TC and their development might be related to the treatment procedures¹⁵. Studies suggest that subclinical hyperthyroidism (due to suppressive hormone therapy) has potential harmful effects on bone metabolism and the cardiovascular system¹⁹ and is even associated with increased mortality due to cardiovascular diseases²⁰. More research is needed into the type, severity and impact of comorbid conditions in TC survivors, the development over time and the associations with treatments²¹.

Our finding that partnered patients and patients with a higher educational level had higher HRQoL scores are in line with previous research^{22, 23}. Partnered patients experience more social support²³ and higher educated patients possibly receive more information by asking more questions, are more satisfied, choose the best doctor for their feeling and have a better understanding of the disease²², that might lead to lower levels of anxiety and depression and better coping strategies.

The strengths of our population-based study are the high response rate, the inclusion of long-term TC survivors (2-20 years after diagnosis), the large sample size, the availability of normative data of the EORTC QLQ-C30 and the use of a TC specific HRQoL questionnaire. However, the present study has the following limitations. First, detailed follow-up treatment data was lacking because the cancer registry registers only the primary treatment procedure. Secondly, patients with unverifiable addresses were younger and more often had stage I papillary tumour compared to the respondents. Therefore our findings cannot be generalized to this younger group of patients with papillary tumours. Furthermore, people from the normative population more often had a higher educational level compared to the TC survivors, which could have influenced our results. The fourth limitation was the cross-sectional study design which limits the determination of causal associations.

Assessment of more specific biochemical (TSH levels and serum free T4, T3) and treatment parameters (levothyroxine dose, extent surgery, additional treatments) in combination with the assessment of THYCA-QoL over time is needed to draw definitive conclusions about the exact mechanisms leading to a decreased HRQoL among long-term TC survivors.

As a consequence of the good prognosis for differentiated TCs, patients are sometimes advised by HCP that TC is not a serious problem²⁴. This attitude trivializes the importance of the disease and causes patients to feel dismissed as not having a serious disease²⁵. Since survivors report decreased HRQoL and several TC specific symptoms long-term after diagnosis, there is a need for multidisciplinary aftercare. The first step for multidisciplinary aftercare will be recognition, recording and acknowledgment of specific long-term health problems of patients with TC by HCPs. Our questionnaire (THYCA-QoL) can be of value in the treatment and after care of TC survivors. It will make HCPs more aware of the potential HRQoL issues TC survivors are dealing with. HCPs can monitor changes in HRQoL (and its determinants) over time and provide continuous support for patients with TC during follow-up surveillance. In addition, HCPs could also help to improve HRQoL among patients with TC by showing them how to manage uncomfortable symptoms and by referring them for further services when necessary (for example physical activity programs or support groups).

In conclusion, TC survivors have a worse HRQoL compared to the normative population. TC specific neuromuscular, sympathetic, concentration and psychological problems last up long-term after diagnosis and are more strongly associated with HRQoL than socio-demographic and clinical factors alone. Awareness of these specific determinants of HRQoL could help health care practitioners to provide better supportive care.

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CHAPTER 12

Fatigue among (long-term) thyroid cancer survivors: results from the population-based PROFILES registry

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Submitted

ABSTRACT

Aim: To obtain insight into the prevalence of fatigue among short-term and long-term thyroid cancer survivors, by comparing a sample of thyroid cancer survivors with an age- and sex-matched normative population. Secondly, our aim was to investigate which demographic, clinical, and thyroid cancer specific characteristics were associated with fatigue.

Methods: All patients diagnosed with thyroid cancer between 1990-2008, as registered in the Eindhoven Cancer Registry, received a cross-sectional survey on fatigue (FAS) and disease-specific symptoms (THYCA-QoL). The fatigue scores were compared with those of an age- and sex-matched normative population (n=530). Multiple linear regression analyses were conducted to investigate the independent associations between clinical and demographic variables and (thyroid cancer specific) HRQoL.

Results: Eighty-six percent (n=306) responded. Short-term survivors and long-term thyroid cancer survivors (< 5 years: 22.6 ± 7.3 ; 5-10 years: 22.6 ± 8.5 ; 10-15 years: 20.9 ± 6.6 ; >15 years: 20.5 ± 6.7) had statistically significant higher scores on fatigue compared to the normative population (18.7 ± 5.9 ; $p < 0.001$). Anxiety (OR: 1.15, 95% CI: 1.03-1.28) and depression (OR: 1.43, 95% CI: 1.22-1.68) were associated with fatigue, as was also the case for thyroid cancer specific neuromuscular (OR: 1.03, 95%CI: 1.01-1.06, $p < 0.01$), concentration (OR: 1.03, 95%CI: 1.01-1.06, $p = 0.01$) and psychological problems (OR: 1.06, 95%CI: 1.02-1.10, $p < 0.01$).

Conclusion: Short-term and long-term thyroid cancer survivors report higher levels of fatigue compared to an age- and sex-matched normative population. Both thyroid cancer specific and mental health problems were strongly associated with fatigue. Future research is needed to determine the underlying mechanisms of fatigue among thyroid cancer survivors and identify possible treatment options.

INTRODUCTION

Worldwide, the incidence of thyroid cancer is rising ¹. As a result of the very good prognosis of papillary and follicular thyroid cancer (exceeding >90% 5-year survival) the number of thyroid cancer survivors is rising ^{2,3}. Treatment of thyroid cancer involves surgery, predominantly (near-)total thyroidectomy, followed by radioiodine (¹³¹I) therapy to ablate the remaining thyroid tissue. Depending on type and size of the tumour hemithyroidectomy could suffice. The removal of the thyroid gland is accompanied by a lifelong dependence on supplement therapy with levothyroxine, in the first 2 years with dosing regimens suppressing thyroid stimulating hormone (TSH) production ^{4,5}, causing subclinical hyperthyroidism. Despite the efficacy of these primary treatments and the high long-term survival rates, the disease can recur even decades later. Therefore, long-term follow-up is necessary. Given the longevity of thyroid cancer patients, the possible long-term effects of cancer and its treatment on patients' well-being are of increasing importance.

Fatigue is a common problem among different groups of cancer survivors, with prevalence rates ranging between 17% and 90% ⁶⁻⁸. High levels of fatigue are associated with low health-related quality of life ⁹ and high levels of emotional distress ¹⁰. Research focusing on the levels of fatigue among thyroid cancer survivors is lacking. Nevertheless, fatigue is a frequently reported complaint among patients with (subclinical) hyperthyroidism ¹¹. Since short-term thyroid cancer survivors receive suppressing doses of levothyroxine, causing subclinical hyperthyroidism, it can be expected that these survivors experience higher levels of fatigue compared to long-term thyroid cancer survivors who have returned to an euthyroid state.

The primary objective of our study was to obtain insight into the prevalence of fatigue among short-term and long-term thyroid cancer survivors, by comparing a sample of thyroid cancer survivors with an age- and sex-matched normative population. Secondly, our objective was to investigate which demographic and clinical characteristics and which thyroid cancer-specific and mental health problems were associated with fatigue in thyroid cancer survivors. Our hypotheses were 1) short-term thyroid cancer survivors report higher levels of fatigue compared to long-term survivors and the normative population; 2) long-term survivors 'return' to normal levels of fatigue and therefore report similar fatigue levels compared to the normative population; 3) clinical and psychological variables are significantly associated with fatigue.

METHODS

Setting and population

This study is a population-based survey among thyroid cancer survivors registered within the Eindhoven Cancer Registry (ECR) of the Comprehensive Cancer Centre South (CCCS). The ECR compiles data of all individuals newly diagnosed with cancer in the southern part of the Netherlands, an area with 10 hospitals serving 2.3 million inhabitants¹². All individuals diagnosed with thyroid cancer between 1990 and 2008 as registered in the ECR were eligible for participation (N=568). We excluded patients who had cognitive impairment or were too ill at time of the study (medical records and advice attending specialist N=31), had unverifiable addresses (N=90), or died prior to the start of the study (according to the ECR, the Central Bureau for Genealogy which collects information on all deceased Dutch citizens via the civil municipal registries, and hospital records; N=6). One hospital declined to participate (N=86). Questionnaires were sent to the remaining 355 patients. This study was approved by the certified Medical Ethics Committee of the Maxima Medical Centre in Eindhoven.

Data collection

Data collection started in November 2010 and was done within PROFILES (Patient Reported Outcomes Following Initial treatment and Long term Evaluation of Survivorship)¹³. PROFILES is a registry for the study of the physical and psychosocial impact of cancer and its treatment from a dynamic, growing population-based cohort of both short and long-term cancer survivors. PROFILES contains a large web-based component and is linked directly to clinical data from the Eindhoven Cancer Registry (ECR). Details of the PROFILES data collection method have been previously described¹³. In summary, survivors were informed of the study via a letter from their (ex-)attending specialist. The letter included a link to a secure website, a login name, and a password, so that interested patients could provide informed consent and complete questionnaires online. If the patient did not have access to internet, or preferred written rather than digital communication, (s)he could return our postcard by mail after which (s)he received our paper-and-pencil version of the informed consent form and questionnaire. Data from the PROFILES registry is available for non-commercial scientific research, subject to study question, privacy and confidentiality restrictions, and registration (www.profilesregistry.nl).

Study measures

Sociodemographic and clinical characteristics

Survivors' sociodemographic and clinical characteristics at time of cancer diagnosis were available from the ECR. The ECR routinely collects data on tumour characteristics, including date of diagnosis, tumour grade and stage according to the Tumour-Node-Metastasis clinical

classification¹⁴, treatment, and patient background characteristics including date of birth and comorbidity at the time of diagnosis. Self-reported comorbidity at the time of survey was categorized according to the adapted Self-administered Comorbidity Questionnaire (SCQ)¹⁵. The SCQ also assesses survivors' perceived burden and medication use for each comorbid condition. Questions on marital status, educational level, and current occupation were added to the questionnaire.

Mental health

Mental health was assessed with the Hospital Anxiety and Depression Scale (HADS), with 7 items each assessing anxiety and depression.¹⁶ Clinical level of anxiety or depressive symptoms was indicated with a score of ≥ 8 on each subscale.^{16, 17}

Thyroid-specific HRQoL

Thyroid cancer specific HRQoL was measured by the THYCA-QoL which was developed to assess side-effects due to thyroid cancer or its treatment.¹⁸ The questionnaire consists of 24 items, with a time frame of the previous week, except for the sexual interest item which is four weeks. Each item is scored on a 4 point response scale ranging from 1, 'not at all' to 4, 'very much'. The THYCA-QoL consists of seven scales (neuromuscular, voice, concentration, sympathetic, throat/mouth, psychological and sensory problems) and six single items. Scores were linear transformed to a 0-100 scale. A higher score on this scale means more complaints.

Fatigue

Fatigue was assessed with the Fatigue Assessment Scale (FAS), a questionnaire consisting of 10 items: five questions reflecting physical fatigue and five questions for mental fatigue. The response scale is a 5-point scale (1 never to 5 always) and scores can range from 10 to 50. The psychometric properties are good^{19 20} and the questionnaire has been used with cancer patients before²¹.

Normative population

Normative population data was obtained from CentERpanel, an online household panel that is representative of the Dutch population. The process of the annual data collection, which started in 2009 by our study group, is described elsewhere²². The most recent data wave in 2011 also included an assessment of fatigue with the FAS. From the 2040 (82%) members of 18 years and older, an age- and sex-matched normative sample (n=530) was selected for this study to reflect the age and sex distribution of the thyroid cancer sample. Sociodemographic data such as marital status, and comorbidity with the SCQ were also collected for this group.

Statistical analyses

Demographic and clinical data of respondents, non-respondents and patients with unverifiable addresses were compared using chi-square statistics for categorical variables and analysis of variance (ANOVA) for continuous variables. The non-parametric Wilcoxon test was applied when normality and homogeneity assumptions of continuous variables were violated.

ANOVA was furthermore used to compare the mean scores of the thyroid cancer sample (stratified by years since diagnosis: short-term <5 years; long-term 5-10 years; long-term 10-15 years; long-term >15 years) on the FAS items and total score with those of the Dutch normative population.

Logistic regression models were conducted to identify associations of demographic and clinical variables, mental health and thyroid cancer specific problems with fatigue. The models were composed as follows: 1) demographics; 2) demographics + clinical variables; 3) demographics + clinical variables + mental health; 4) demographics + clinical variables + thyroid specific HRQoL.

The total FAS score was divided into two groups, 10 to 21 (not fatigued), 22-50 (fatigued) as previously done ²³.

Clinically meaningful differences were determined with Norman's 'rule of thumb', whereby a difference of ≈ 0.5 SD indicates a threshold of discriminant change in scores of a chronic illness ²⁴. All statistical analyses were performed using SPSS version 17.0 (Statistical Package for Social Sciences, Chicago, IL, USA) and P values <.05 were considered statistically significant.

RESULTS

Patient and tumour characteristics

Three hundred and six patients returned a completed questionnaire (response 86%). A comparison of respondents, non-respondents and patients with unverifiable addresses indicated that patients with unverifiable addresses were younger compared to non-respondents and respondents (mean 52, 56 and 54 years respectively) ²⁵. No differences between groups were seen regarding sex, type of thyroid cancer, stage of the disease or primary treatment.

The mean age at time of the survey was 56 (SD=15) years. Average time since diagnoses was 9.6 (SD= 5.5) years. More than half of the patients were diagnosed with stage I disease (57%). Surgery (99%) was followed by iodine-131 ablation therapy in 69% and by radiotherapy in 3% of the cases. More than three quarters (78%) of the patients had one or more comorbid conditions.

Table 1: Clinical and socio-demographic characteristics of thyroid cancer survivors stratified by time since diagnosis and the normative population (n (%))

	Short-term survivors <5 years (n=81)	Long-term survivors 5-10 years (n=86)	Long-term survivors 10-15 years (n=75)	Long-term survivors >15 years (n=64)	Normative population (n=530)	p-value
Mean age at time of survey (±SD)	55.6 ± 16.0	54.5 ± 14.8	56.8 ± 13.1	59.6 ± 13.4	55.8 ± 14.6	0.26
Mean years since initial diagnosis (±SD)	3.3 ± 0.9	7.3 ± 1.5	12.1 ± 1.5	17.8 ± 1.8	n.a.	<0.001
Sex						0.95
Male	20 (25)	24 (28)	17 (23)	15 (23)	132 (25)	
Female	61 (75)	62 (72)	58 (77)	49 (77)	397 (75)	
Type of thyroid cancer						0.15
Papillar	63 (80)	58 (67)	55 (73)	42 (66)	n.a.	
Follicular (including Hurthle cell)	13 (17)	23 (27)	20 (27)	17 (27)		
Medullar	3 (4)	5 (6)	-	5 (8)		
Primary treatment						0.24
Surgery alone	19 (24)	26 (30)	22 (29)	16 (25)	n.a.	
Surgery + iodine-131 ablation	59 (73)	59 (69)	51 (68)	43 (67)		
Surgery + radiotherapy	3 (4)	-	1 (1)	5 (8)		
Other (chemotherapy/radiotherapy or no oncological treatment)	-	1 (1)	1 (1)	-		
Stage						<0.001
1	34 (43)	54 (64)	41 (57)	43 (68)	n.a.	
2	11 (14)	14 (17)	18 (25)	16 (25)		
3	22 (28)	12 (14)	11 (15)	3 (5)		
4	12 (15)	5 (6)	2 (3)	1 (2)		
Comorbidity at time of study						0.01
None	19 (24)	29 (34)	17 (23)	16 (25)	215 (41)	
1	26 (32)	24 (28)	24 (32)	18 (28)	128 (24)	
≥ 2	36 (44)	33 (38)	34 (45)	30 (47)	188 (35)	
Partner						0.28
Yes	58 (72)	69 (80)	62 (83)	49 (77)	389 (73)	
No	23 (28)	17 (20)	13 (17)	15 (23)	142 (27)	
Educational level ^a						<0.001
Low	5 (6)	11 (13)	9 (12)	8 (13)	20 (4)	
Medium	50 (62)	49 (58)	49 (65)	44 (69)	315 (60)	
High	26 (32)	25 (29)	17 (23)	12 (19)	194 (37)	
Employment status						0.29
Yes	40 (50)	48 (57)	40 (54)	26 (42)	250 (47)	
No	40 (50)	36 (43)	34 (46)	36 (58)	281 (53)	

Some variables exceed 100% due to rounding off; some variables do not add up to 100% due to missing data.

^a Education: Low (no or primary school); Medium (lower general secondary education or vocational training); High (pre-university education, high vocational training, university; n.a.: these items were not assessed in the normative population)

Table 2: Mean scores (\pm SD) of thyroid cancer specific problems and mental health problems stratified by time since diagnosis and the normative population

	Short-term survivors <5 years (n=81)	Long-term survivors 5-10 years (n=86)	Long-term survivors 10-15 years (n=75)	Long-term survivors >15 years (n=64)	Normative population (n=530)	p-value
Thyroid cancer specific complaints						
Neuromuscular problems	27.7 \pm 22.1	23.8 \pm 23.3	22.5 \pm 20.4	21.6 \pm 21.3	n.a.	0.35
Voice problems	16.0 \pm 22.7	12.1 \pm 20.6	9.0 \pm 15.7	5.2 \pm 11.7		0.006
Concentration problems	19.6 \pm 21.5	18.5 \pm 25.2	12.1 \pm 19.3	12.1 \pm 18.5		0.06
Sympathetic problems	23.3 \pm 29.2	21.8 \pm 28.3	14.4 \pm 20.5	13.6 \pm 19.7		0.04
Throat/mouth problems	19.3 \pm 20.1	13.2 \pm 18.1	12.3 \pm 15.3	4.8 \pm 8.0		<0.001
Psychological problems	16.9 \pm 17.1	15.8 \pm 18.7	12.9 \pm 16.1	10.7 \pm 12.4		0.12
Sensory problems	17.5 \pm 19.2	14.3 \pm 19.8	14.1 \pm 18.9	14.3 \pm 21.2		0.66
Mental health						
HADS anxiety	5.2 \pm 3.6	5.1 \pm 4.4	4.1 \pm 3.2	4.2 \pm 3.7	3.7 \pm 3.3	0.001
HADS depression	3.6 \pm 2.9	3.7 \pm 3.5	3.0 \pm 2.6	3.4 \pm 3.2	3.6 \pm 3.3	0.66
<i>% above the ≥ 8 clinical cut-off^{16, 17}</i>						
HADS anxiety	19 (24)	20 (24)	8 (12)	8 (14)	64 (12)	0.004
HADS depression	11 (14)	13 (16)	5 (7)	7 (12)	7 (12)	0.60

n.a.: these items were not assessed in the normative population

Comparisons on clinical and socio-demographic characteristics, thyroid cancer specific and mental health problems of respondents stratified by years since diagnosis showed that short-term survivors were more likely to be diagnosed with a higher stage disease compared to long-term survivors (Table 1). Furthermore, survivors <5 years since diagnosis were more likely to report voice, sympathetic and throat/mouth problems compared to survivors >15 years since diagnosis and higher levels of anxiety compared to survivors ≥ 10 years since diagnosis (Table 2). There was a trend toward diminishing thyroid cancer specific problems over time.

The normative population was more likely to be higher educated, reported less comorbidities and were less likely to have anxiety compared to short-term and long-term thyroid cancer survivors (Tables 1 and 2).

Fatigue of thyroid cancer survivors compared with a normative population

In general, short-term survivors reported the highest levels of mean fatigue scores and the normative population, the lowest (Table 2).

The normative population was significantly less likely than the survivors group to report being bothered by fatigue, getting tired quickly, not being able to do much, feeling exhausted physically and mentally, problems with starting things and thinking clearly, and no desire to do anything. Also, the FAS total score was significantly lower for the normative population

compared to the thyroid cancer survivors. No significant differences were found between short- and long-term survivors.

Clinically meaningful differences between the normative population and the short-term survivors were found for the items getting tired very quickly, feeling physically exhausted, problems with thinking clearly and the FAS total score. Furthermore, a clinically meaningful difference was found between long-term survivors (5-15 years after diagnosis) and the normative population for the item getting tired very quickly. Comparison between short- and long-term survivor groups showed no clinically meaningful differences in fatigue scores (Table 3).

When stratified by time since diagnosis and divided into three fatigue groups; not fatigued (as defined by a score of 10 to 21 on the FAS), fatigued (22 to 34), and very fatigued (35 to 50) as previously done ²³, significant differences were noted between all the survivors (Figure 1) and the normative population ($p < 0.001$). Survivors were more often classified as fatigued or very fatigued (short-term: 43%; long-term 5-10 years: 44%; long-term 10-15 years: 47%; long-term > 15 years: 39%) compared to the normative population (25%). Furthermore long-term survivors > 15 years after diagnoses reported less fatigue compared to the other three survivor groups, and survivors < 10 years after diagnosis reported more often to be very fatigued compared to survivors ≥ 10 years after diagnosis ($p = 0.03$).

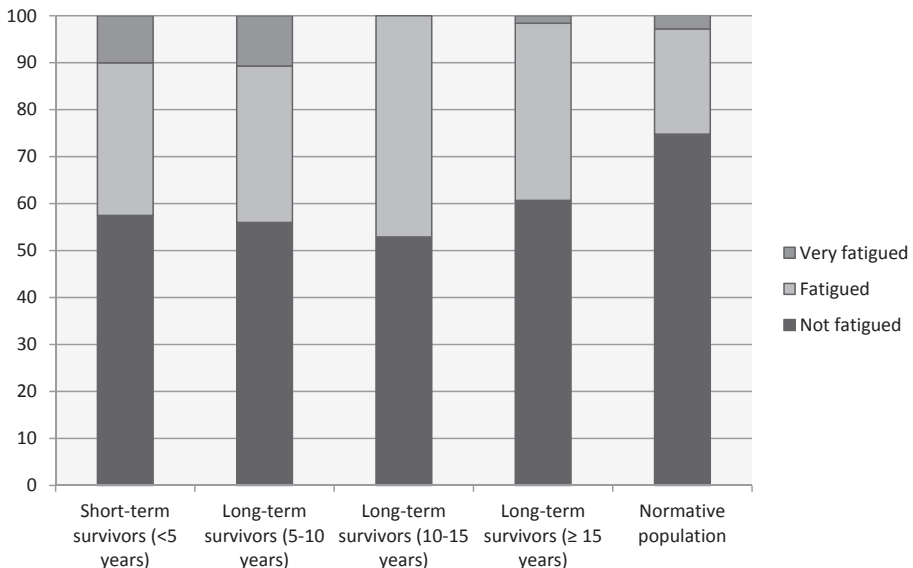


Figure 1: Fatigue levels of thyroid cancer survivors compared to an age and sex-matched normative population

% Thyroid cancer survivors stratified by years since diagnosis (short-term: < 5 years; long-term: ≥ 5 years), and normative population who are fatigued. Category cut-offs were based on FAS total scores: not fatigued (10-21), fatigued (22-34), very fatigued (35-50).

Significant differences were noted between the survivors and normative population ($p < 0.001$).

Table 3: Mean fatigue scores of thyroid cancer survivors by years since diagnosis and the normative population

FAS items (range: 1-5)	Short-term survivors <5 years (n=80)	Long-term survivors 5-10 years (n=84)	Long-term survivors 10-15 years (n=72)	Long-term survivors >15 years (n=60)	Norm (n=530)		p-value
					All survivors	Norm + all survivors	
1. I am bothered by fatigue	2.7±1.1	2.8±1.2	2.7±1.2	2.5±1.0	2.1±0.9	0.45	<0.001
2. I get tired very quickly	2.6±1.2 ^a	2.6±1.3 ^a	2.4±1.1 ^a	2.3±1.1	1.9±0.9	0.46	<0.001
3. I do not do much during the day	2.2±1.1	2.3±1.3	1.9±1.0	2.0±1.1	1.8±0.9	0.14	<0.001
4. I have enough energy for everyday life ^b	2.9±1.3	2.7±1.3	2.7±1.3	2.5±1.3	2.6±1.3	0.51	0.43
5. Physically, I feel exhausted	2.1±1.0 ^a	2.0±1.1	1.9±0.9	1.8±0.9	1.6±0.8	0.49	<0.001
6. I have problems starting things	2.0±0.9	2.0±1.1	1.8±0.7	1.9±0.9	1.7±0.8	0.43	0.01
7. I have problems thinking clearly	1.9±0.9 ^a	1.8±1.1	1.6±0.6	1.7±0.7	1.4±0.7	0.08	<0.001
8. I feel no desire to do anything	2.0±0.8	2.0±1.0	1.8±0.7	2.0±0.8	1.7±0.7	0.47	<0.001
9. Mentally, I feel exhausted	1.8±0.9	1.8±1.1	1.6±0.7	1.6±0.8	1.5±0.7	0.19	<0.001
10. When I am doing something, I can concentrate quite well ^b	2.5±1.2	2.6±1.3	2.5±1.3	2.3±1.2	2.4±1.3	0.62	0.52
FAS mean total score	22.6±7.3 ^a	22.6±8.5	20.9±6.6	20.5±6.7	18.7±5.9	0.20	<0.001

Higher scores indicate higher levels of fatigue

^aClinically meaningful difference based on Norman's rule of ≥ 0.5 SD²⁴ detected between indicated group and the normative population.^bReversed items

Logistic regression

Logistic regression models were conducted to identify associations of demographic and clinical variables, mental health and thyroid cancer specific problems with fatigue. Model 1 consisting of only demographic variables showed that lower education (odds ratio (OR): 2.79, 95% confidence interval (CI): 1.55-5.04, $p<0.01$) was associated with a higher risk for fatigue (Table 4).

With the inclusion of clinical variables in Model 2, education remained significantly associated with fatigue, while partnership became significant in this model, whereby absence of a partner was associated with more fatigue (OR: 1.94, 95% CI: 1.05-3.58, $p=0.04$). Having comorbid conditions (OR: 2.60, 95% CI: 1.42-4.74, $p<0.01$) was also significantly associated with fatigue.

In Model 3, anxiety (OR: 1.15, 95%CI: 1.03-1.28, $p=0.01$) and depression (OR: 1.43, 95%CI: 1.22-1.68, $p<0.01$) were significantly associated with fatigue. Following the inclusion of these psychological factors, only comorbidity (OR: 2.39, 95%CI: 1.14-5.00, $p=0.02$) remained significant in this model.

In Model 4, neuromuscular (OR: 1.04, 95%CI: 1.02-1.06, $p<0.01$), concentration (OR: 1.03, 95%CI: 1.01-1.06, $p=0.01$) and psychological problems (OR: 1.05, 95%CI: 1.02-1.28, $p<0.01$) were significantly associated with fatigue, whereby more problems indicated higher levels of fatigue. All clinical variables were not significantly associated with fatigue anymore, while age at survey (OR: 0.97, 95%CI: 0.94-1.00, $p=0.05$) and educational level (OR: 2.57, 95%CI: 1.06-6.62, $p=0.04$) were also significant, whereby an older age and higher educational level were associated with less fatigue. The single items of the thyroid cancer specific HRQoL questionnaire (problems with scar, felt chilly, tingling hands and/or feet, headaches, gained weight) were not related to fatigue, except for sexual functioning (OR: 0.98, 95%CI: 0.97-1.00, $p=0.05$), whereby less interest in sex was related to higher levels of fatigue.

DISCUSSION

This large population-based study among survivors of thyroid cancer showed that fatigue remains a problem long-term after diagnosis. In general, regardless of time since diagnosis, thyroid cancer survivors reported statistically significant higher levels of fatigue when compared with an age- and sex-matched normative population, although clinically meaningful differences were only found between short-term survivors and the normative population. Levels of fatigue decreased with increasing time since diagnosis, but these differences were not significant. Thyroid cancer specific (neuromuscular, concentration and psychological) and mental health problems were most strongly associated with fatigue.

Table 4: Logistic models of factors associated with fatigue

	Model 1 (demographics)	Model 2 (Model 1 + clinical)	Model 3 (Model 2 + mental health)	Model 4 (Model 2 + thyroid specific symptoms)
	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)
Block 1 (demographic variables)				
Age at survey	0.99 (0.97-1.01)	0.99 (0.97-1.01)	0.98 (0.95-1.01)	0.97 (0.93-1.00)*
Sex	1.21 (0.69-2.12)	0.99 (0.55-1.18)	1.54 (0.68-3.49)	0.60 (0.23-1.56)
Educational level	2.79 (1.55-5.04)**	2.68 (1.46-4.93)**	2.09 (0.99-4.38)	2.57 (1.06-6.62)*
Marital status	1.77 (0.98-3.18)	1.94 (1.05-3.58)*	1.38 (0.62-3.07)	1.00 (0.39-2.56)
Block 2 (clinical variables)				
Time since diagnosis		0.99 (0.94-1.04)	1.03 (0.97-1.09)	1.01 (0.93-1.09)
Comorbidity		2.60 (1.42-4.74)**	2.39 (1.14-5.00)*	1.47 (0.58-3.73)
Stage of cancer		1.01 (0.51-2.0)	0.90 (0.38-2.15)	0.55 (0.18-1.75)
Treatment		1.23 (0.70-2.17)	1.12 (0.57-2.24)	0.95 (0.42-2.18)
Block 3 (mental health)				
HADS anxiety			1.15 (1.03-1.28)*	
HADS depression			1.43 (1.22-1.68)**	
Block 4 (thyroid cancer specific problems)				
Neuromuscular problems				1.03 (1.01-1.06)**
Voice problems				1.01 (0.99-1.03)
Concentration problems				1.03 (1.01-1.06)*
Sympathetic problems				1.02 (0.99-1.04)
Throat/mouth problems				1.00 (0.97-1.02)
Psychological problems				1.06 (1.02-1.10)**
Sensory problems				1.00 (0.98-1.02)

OR: odds ratio; CI: confidence interval. Only significant OR is reported.

Fatigue: not fatigued (10-21) vs. fatigued (22-50).

Continuous variables: time since diagnosis, age at survey, anxiety, depression and thyroid cancer specific problems

Sex=Male (reference) vs. female; Educational status= high (reference) vs. medium/low; Marital status= partner (reference) vs. no partner; Comorbidity= no comorbidity (reference) vs. one or more comorbidities; Stage= 1,2 (reference) vs. 3,4; Treatment = surgery (reference) vs. surgery + additional therapy.

*p<0.05; **p<0.01

Our results are consistent with findings of a recent German study showing that thyroid cancer patients at the beginning of inpatient rehabilitation do suffer from higher levels of fatigue than the general population ²⁶, as was also found in a Korean study among short-term thyroid cancer survivors (median 2.7 years after diagnosis) ²⁷. A Dutch study among cured differentiated thyroid cancer patients (median duration of cure of 6.3 years) showed that a longer duration of cure was correlated with better scores on general, mental and physical fatigue ²⁸. Our results also show decreasing levels of fatigue with increasing years since diagnoses, however levels of fatigue of long-term survivors were higher compared to the normative population albeit not clinically relevant higher.

The high doses of replacement therapy (TSH < 0.1 mU/L) in the first years of follow-up, for patients who underwent ablation therapy or had high risk of recurrence, and the subsequent TSH suppression, may cause symptoms of (subclinical) hyperthyroidism. Subclinical hyperthyroidism is a reversible cause of fatigue ¹¹. However, after the first years, the doses of replacement therapy will be lowered for low risk survivors (TSH level around median (1 mU/L)) to restore euthyroidism and fatigue levels are therefore expected to decrease. This might explain the decrease in fatigue levels for long-term survivors compared to short-term survivors in our study. However, the long-term survivors still had statistically significant higher fatigue levels compared to the normative population. This is in contrast with another Dutch study showing that thyroid cancer patients (n=24) under long-term subclinical hyperthyroidism (> 10 years) do not differ in the levels of general, mental and physical fatigue compared to an age- and sex matched reference group ²⁹. Our finding that thyroid cancer specific problems were associated with fatigue could indicate that the TSH level of around 1 mU/L, might not be the optimal (pre-operative) level for the specific patient ³⁰, and that the patient therefore does not feel well.

Another explanation of our findings could be the presence of cancer-related fatigue (CRF). Fatigue levels of thyroid cancer survivors (43%) are comparable to those observed in other cancer survivor populations (17-90%)^{6, 8, 31}. According to the guidelines of the National Comprehensive Cancer Network (NCCN), cancer-related fatigue is defined as a distressing, persistent, subjective sense of physical, emotional, and/or cognitive tiredness or exhaustion related to cancer or its treatment that is not proportional to recent activity and interferes with usual functioning ³². The underlying mechanisms involved in cancer-related fatigue are not well understood. Possible mechanisms include effects of cancer or its treatment on the central nervous system, muscle energy metabolism, sleep rhythms ³³, mediators of inflammation and stress ³⁴, immune activation ³⁵, and hormonal changes related to effects on the hypothalamic–pituitary axis ⁷. A Norwegian study showed that type or intensity of cancer treatment is unrelated to the level of cancer-related fatigue and more related to

mental and somatic health problems³⁶. This finding is in line with the results of a Dutch study showing that levels of fatigue of thyroid cancer survivors (median duration of cure of 6.3 years) were not affected by initial tumour stage, total activity of radioiodine, tumour recurrence, and replacement therapy dose²⁸. In addition to this, our own results show no associations between clinical factors and fatigue (except for comorbidity), while thyroid cancer specific and mental health problems were most strongly associated with fatigue.

Due to the high prevalence of fatigue and the profound effect that it can have on a patient's daily life, healthcare providers should be encouraged to inquire about the presence of this symptom³⁷. Both non-pharmacologic and pharmacologic treatments are available for the treatment of cancer-related fatigue. Currently, the best treatments are psychosocial interventions and exercise³⁷. Other non-pharmacologic and pharmacologic interventions have less supporting evidence but still may be effective for some patients. Recently, an Internet-based education program based on NCCN guidelines showed good results to help patients manage cancer-related fatigue³⁸. Further research is needed to determine if an intervention for fatigue can reduce the high levels of fatigue among long-term thyroid cancer survivors.

The present study has some limitations that should be mentioned. Although demographic and clinical information of non-respondents and survivors with unverified addresses were available for comparison, the health status of these survivors and its possible effects on current results remain unknown. In addition, the cross-sectional study design limits the determination of causal association between cancer-related factors and fatigue. A logistic regression model including mental health and thyroid cancer specific problems could not be performed, since there is a high correlation between the thyroid cancer specific psychological problem scale and the anxiety scale of the HADS. Therefore, it was not possible to determine which of the factors was most strongly associated with fatigue.

Nevertheless, the present study provides an important contribution to the limited data available on fatigue of (long-term) thyroid cancer survivors. Since our study has a high response rate, extrapolating these results to the larger population of thyroid cancer survivors seems justified. Furthermore, we were able to compare fatigue levels with an age- and sex-matched normative sample. Future research with longitudinal designs should make use of an additional reference group, namely a group of patients with hyperthyroidism without thyroid cancer, to see whether it is the history of thyroid cancer accompanied by CRF or (subclinical) hyperthyroidism that causes the higher levels of fatigue compared to the normative population.

In conclusion, about 40% of the thyroid cancer survivors report a high level of fatigue up till 20 years after diagnosis. Short-term and long-term thyroid cancer survivors report higher

levels of fatigue compared with the normative population. Thyroid cancer specific and mental health problems were highly associated with fatigue. Further research is needed to explore the underlying determinants of fatigue and the optimal treatment options for fatigue among thyroid cancer survivors.

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CHAPTER 13

Summary and General discussion



SUMMARY OF RESULTS

In this chapter, the main findings of this thesis are summarized, and put into a perspective, whereby conceptual and methodological considerations and implications for clinical practice and future research will be discussed.

Part I: Information provision and patient reported outcomes

The summary of part I will be guided by the conceptual model presented in the general introduction (Figure 1). At the centre of the conceptual model is the perceived level of, and satisfaction with the received information. Throughout this thesis information provision was defined as all cancer-related information provided by the health care provider (HCP) in oral, written or any other form. Our first aim was to assess the levels of received information and the satisfaction with this information among melanoma cancer survivors (**Chapter 2**). We used the internationally validated EORTC QLQ-INFO25 to assess information provision¹. Melanoma survivors indicated that they received no information about different aspects of their disease (9-37%), treatment (38%), and aftercare (84-94%). More than half of the survivors (61%) were not or only a bit satisfied with the amount of information received; a quarter of the patients indicated that they wanted to receive more information.

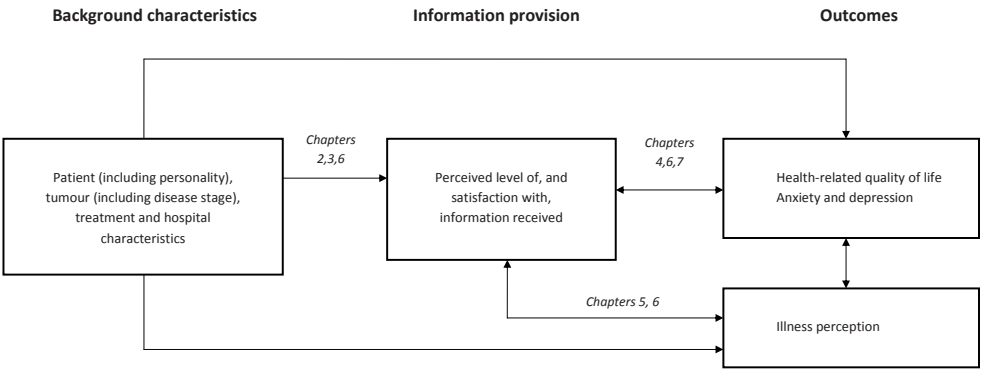


Figure 1: Conceptual model of relations between information provision and clinical, socio-demographic, psychological and patient reported outcomes.

The left part of our conceptual model indicates that several background characteristics might be associated with the perceived level of and satisfaction with the received information. Among melanoma survivors the perceived receipt of information was associated with a higher disease stage, less years since diagnosis, a higher educational level and younger age, while satisfaction with information was associated with hospital of treatment, a higher educational level and use of the internet (**Chapter 2**).

Besides the associations of clinical and socio-demographic factors with information provision, psychological factors like personality can also affect the perceived level of received information. Therefore the effects of the personality traits negative affectivity (NA) and social inhibition (SI) and their combined effect (Type D personality) on satisfaction with received information among a diverse group of 3080 cancer survivors were examined (**Chapter 3**). The perceived receipt of information, and the satisfaction with and usefulness of the received information were all lower for cancer survivors with a Type D personality compared to cancer survivors without a Type D personality or survivors with high scores for NA or SI only, also after controlling for clinical and socio-demographic characteristics.

In the right part of our conceptual model it is hypothesized that several patient reported outcomes (PROs) could have a bidirectional relationship with the perceived level of, and satisfaction with the received information. In **Chapter 4**, the literature on the relationship between information provision and health-related quality of life (HRQoL), anxiety and depression was systematically reviewed. This review showed that satisfied patients, patients with fulfilled information needs, and patients who experience less information barriers, in general have a better HRQoL and lower levels of anxiety and depression. Most of these findings are based on observational studies. Only one intervention study which aimed to improve information provision showed a positive relation with HRQoL, while the other seven intervention studies did not found an association.

To investigate potential pathways between information provision and PROs as observed in the systematic review we hypothesized that illness perception might play an important role. It has been reported that illness perception is a major determinant of HRQoL² and is possibly associated with information provision, which was examined in **Chapter 5**. Results showed that among a diverse group of 3080 cancer survivors the perceived receipt of more *disease-specific* information was associated with more control and a better understanding of the illness, while the perceived receipt of more information *about other services* was associated with more negative consequences of the illness on the patients' life, longer perceived duration of illness, less treatment control, more symptoms attributable to the illness, less understanding of, and stronger emotional reaction to the illness. Satisfaction with the received information was associated with better illness perception on all subscales, except for personal control.

In **Chapter 6**, we brought together the associations between information provision, illness perception and PROs among colorectal cancer (CRC) patients. It was shown that the perceived receipt of information was quite comparable between CRC patients with and without metastasis, except for information about treatments which was higher for patients with metastasized disease. Issues related to disease course and supportive care were mentioned most frequently as topics that CRC patients with metastatic disease wanted to

receive more information about. Only 60% of the patients with metastatic CRC were (quite) satisfied with the received information. For patients with metastasized CRC the perceived receipt of more *disease* information and information about *other services* was associated with worse PROs (illness perception, HRQoL, anxiety and depression), while *satisfaction* with the received information was not associated with PROs.

Most studies described in our systematic review had a cross-sectional design. Therefore, we prospectively examined the relationship between information provision and HRQoL, anxiety and depression among lymphoma and multiple myeloma (MM) (**Chapter 7**). We observed that the perceived receipt of information decreased slightly over time (mostly among short-term survivors), while HRQoL, anxiety and depression levels did not change. Satisfaction with the received information at baseline predicted HRQoL 2 years later, however after correction for baseline HRQoL the relationship largely disappeared. Stability of satisfaction with the received information was associated with better mental HRQoL compared to fluctuating satisfaction levels or stable dissatisfaction with the received information, also when adjusted for baseline HRQoL levels.

Part II: Thyroid cancer survivors: an understudied group

Long-term trends in incidence, mortality, and survival of thyroid cancer (TC) in The Netherlands between 1989 and 2009 were examined in **Chapter 8**. Since 1989 the incidence of TC increased significantly in the Netherlands, while mortality from TC decreased. Five-year relative survival rates remained stable and appeared to be somewhat higher in the 2004-2009 period compared to earlier periods, except for advanced tumours of which the frequency decreased markedly. Due to the increasing incidence and good prognosis of differentiated TC, the number of (long-term) TC survivors is rapidly increasing. The results of this study therefore support the need for research into the long-term HRQoL of TC survivors and possible physical and psychosocial problems survivors' are dealing with after the completion of primary treatment.

In **Chapter 9**, the available literature was systematically reviewed to provide a complete overview on the current knowledge about HRQoL of TC survivors. This review showed that TC survivors report severe impairments of HRQoL after treatment (surgery, radioactive iodine ablation, supplemental thyroid hormone therapy) and follow-up procedures. Studies focusing on long-term TC survivors showed contradictory results. Therefore, strong conclusions on the HRQoL among long-term TC survivors could not be drawn from the studies included in our systematic review. The main problem of included studies was the absence of a valid, TC specific instrument to assess HRQoL. Most studies used a general HRQoL questionnaire, which cannot capture the specific complaints associated with TC and its treatment. This finding resulted in the need to develop a thyroid cancer specific HRQoL questionnaire, which was described in **Chapter 10**. Potentially relevant issues were identified

by our systematic literature review, a focus group meeting, and an issue list completed by six health care providers (HCP) and 18 TC survivors. Resultant issues were analyzed on importance and relevance by HCP and patients which resulted in a provisional list of 30 items formulated as questions according to the EORTC format. Pretesting by a large group of TC survivors led to a selection of 24 items with a good range of response. This resulted in the THYCA-QoL containing 24 items and seven conceptual scales (neuromuscular, voice, concentration, sympathetic, throat/mouth, psychological and sensory problems).

The THYCA-QoL provided the possibility to assess TC specific HRQoL among long-term TC survivors. Using this questionnaire, the long-term HRQoL effects of TC and its various treatments was examined, by comparing a sample of TC survivors (2-20 years since diagnosis) with an age- and gender-matched normative population (**Chapter 11**). Our findings showed that TC survivors report lower levels of physical and psychosocial functioning, and more problems (fatigue, dyspnea, insomnia and financial) compared to an age- and gender matched normative population. Most differences were of small clinical importance. Clinical and socio-demographic factors explained only a small part of the variance in HRQoL, while TC specific neuromuscular, concentration, sympathetic and psychological problems explained a large part (41-58%) of the variance in HRQoL.

Fatigue is a common problem among patients with (subclinical) hyperthyroidism ³, as is the case for TC survivors with suppressing doses of levothyroxine in the first years after surgery. Research focusing on the levels of fatigue among thyroid cancer survivors is lacking. Therefore, we examined the prevalence of fatigue among short-term and long-term TC survivors (**Chapter 12**). Our results showed that around 40% of the TC survivors report a high level of fatigue up till 20 years after diagnosis. Short-term and long-term TC survivors report higher levels of fatigue compared with the normative population, however differences were only clinically meaningful for short-term survivors compared with the normative population. TC specific (neuromuscular, concentration and psychological) and mental health (anxiety and depression) problems were highly associated with fatigue.

GENERAL DISCUSSION

With the ongoing improvements in early detection and treatment of cancer along with the ageing of the population, the number of cancer survivors is rapidly increasing in the Western world. Therefore, achieving and maintaining optimal well-being must be an important objective of current cancer treatment, cancer rehabilitation and aftercare. Adequate information provision is one of the most important factors in the supportive care for cancer survivors and is associated with positive patient reported outcomes (better HRQoL, lower levels anxiety and depression, positive illness perception). Although the knowledge about cancer survivorship has grown in the past decade, survivors of rare tumours, like thyroid cancer (TC), so far received little attention in the cancer survivorship literature.

Growing number of thyroid cancer survivors

Since 1989 the incidence rates of TC increased significantly in The Netherlands, while mortality from TC decreased. These trends caused a marked increase in the number of TC survivors (20-year prevalence of 2700 in 1990 vs. 5500 in 2010). There is an ongoing discussion in the literature about the question whether or not the observed increase in TC incidence is real or apparent. Since the beginning of the 1980's there is an increase in use of more precise diagnostics, like ultrasonography and fine needle aspiration biopsies ⁴, ⁵, and better medical surveillance ⁶. An American study showed a significant decrease in tumour size over time and concluded that the apparent increase in TC incidence was due to increased detection of subclinical disease ⁷. This finding is supported by the finding of a 36% incidence of occult papillary tumours in Finnish adults at autopsies ⁸. It might therefore be possible that the increased incidence of TC in the Netherlands is partly due to overdiagnosis of clinically irrelevant cancer ⁹. Most patients with cytological indeterminate nodules are referred for diagnostic thyroid surgery, but the majority prove to have benign disease ¹⁰ and for these patients surgery is unnecessary ¹¹. The main problem of overdiagnosis is that patients cannot benefit from "unnecessary" treatment, however this treatment can lead to morbidities and can affect the persons' well-being for the rest of his/her life ⁹. Furthermore, increased detection of small tumours can lead to an overestimation of treatment efficacy and a subsequent rise in use of treatment ¹² ¹³. A recent study showed that implementation of a gene-expression classifier to identify a subpopulation of patients with a low likelihood of cancer leads to a marked reduction (74% to 7.6%) in the HCPs decision to operate on cytologically indeterminate thyroid nodules ¹¹ ¹⁴. More clinical strategies should be developed to minimize overdiagnosis.

The increase in incidence rates cannot be completely ascribed to improved detection. Real increases in incidences of TC have been associated with different risk factors (radiation exposure¹⁵⁻¹⁷, low iodine intake ¹⁸ and overweight ¹⁹), although the exact etiology of TC remains unclear and needs to be explored ²⁰.

Current state of information provision among cancer survivors

As the number of cancer survivors is rapidly increasing, investigating the current state of information provision and the degree of satisfaction with received information is important. It reveals whether information provision is sufficient, or whether improvements are needed. Our studies among cancer survivors of different cancer types (melanoma, endometrial, colorectal, (non-)Hodgkin and multiple myeloma) indicate that survivors received quite a bit of information about their disease, medical tests and treatment ^{21,22}. However, a substantial percentage of the survivors stated that they were not or only a little informed about the cause of their disease and possible side effects of their treatment. Cancer survivors received the least information on topics related to aftercare, such as what to expect in their social and sexual life, where to go for additional help, rehabilitation, or psychological support, and how to cope with cancer at home, different care locations outside the hospital, or things to do to improve their health. Moreover, 15 - 28% of the survivors wanted to receive more information, and the most frequently mentioned topics were (psychosocial) aftercare, cause and course of the disease and late effects of treatment. Topics that survivors wanted to receive more information about changed over time, with information about disease stage, treatment options and side-effects of treatment most frequently mentioned in the diagnosis and treatment phase, while post-treatment, patients report a continued need for treatment related information and also information about rehabilitation was important ²³. Survivors who were not satisfied with the received information, indicated on all information provision subscales that they received less information and found the information less helpful than satisfied survivors. Moreover, unsatisfied survivors indicated that they wanted to receive more additional information than satisfied survivors. However, a small group of unsatisfied survivors indicated that they wanted to receive less information than satisfied survivors. Although most patients prefer to be fully informed ²³, a minority of patients do not want to receive all available information ²⁴.

Patient and clinical characteristics and perceived level of received information

Several factors contribute to differences in the perceptions of the received information (left part conceptual model; Figure 1).

Clinical factors associated with perceived levels of information

Levels of perceived information differed between survivors with different types of cancer, possibly due to differences in intensity of treatment and follow-up procedures. Survivors with a higher stage disease and survivors who underwent more advanced treatments (radiotherapy and chemotherapy) perceived to receive more information ^{21,22}. It is likely that HCPs provide more information to these patients, as the treatment is more complex and can have more serious acute and long-term effects than surgery alone. Furthermore, patients

undergoing more advanced treatment often receive information from more than one HCP. In addition, cancer survivors who were diagnosed and treated shortly before the start of our studies reported that they received more information compared to long-term survivors. Patients who are still under supervision of a HCP might have a clearer picture of the information they received. The diminishing contacts of patients with their HCP after the completion of treatment and follow-up could lead to less information exchange ²⁵. It is also possible that recall bias influenced these findings. Patients may forget information they received, because it is often complex and emotionally charged ²⁶.

Except for melanoma survivors, cancer survivors with fewer comorbid conditions reported that they received more information and were more satisfied with the information. One explanation is that patients with more comorbid conditions have more specific information needs that are possibly not fulfilled by the information provided to them.

Moreover, the satisfaction and helpfulness of the received information and the amount of written information received varied between patients treated in different hospitals in our area. This suggests that some hospitals and/or HCPs gave better patient-centred information or additional written information (patient information leaflets), which promotes information recall and understanding.

Socio-demographic factors associated with perceived levels of information

An association between younger age and more perceived information was observed, which is consistent with previous research ²⁷. Studies have shown that older patients tend to ask fewer questions during their visit with their HCP, and might therefore receive less information ^{28, 29}. Older patients appear to be less interested in detailed information, but have a preference for information about the most important aspects of their disease and treatment ²⁹. The acquisition of detailed disease information might not be the main goal of older patients. They often leave the provision of details up to their HCP and therefore have a more passive role, leading to a doctor-centred interaction ³⁰. Older patients have been found to have a greater reliance on information provided by their HCP ²³. Health care providers might also be prejudiced against older patients; some HCPs seem to provide older patients with less information ³¹. Finally, older patients may have more difficulties processing and remembering medical information they receive than younger patients ³². We did not find a relation between gender and levels of received information, while another study showed that women seek more information than men ²³.

Also, survivors with a high educational level indicated that they received more information than lower educated survivors. Previous studies have shown that higher educated patients want as much information on prognosis as possible ³³, are more likely to seek information from a greater range of sources (like the internet) ²³, obtain more information, and show more perceived uncertainty ³⁴. For these reasons, higher educated survivors might ask their

HCPs for more explanation when the provided information does not yet meet their needs ²⁸. It is also possible that HCPs (who are higher educated themselves) are more prone to give more information to patients with a similar educational level. Higher educated patients may also be better able to understand and remember the information.

In addition, survivors who have a partner indicated that they received more information about their disease. Previous research indicates that accompanied patients are likely to benefit from the extra information that their companions remember ³⁵. Discussing the received information with their partner may help patients to better understand and remember the information they receive from their HCP. The presence of companions has been found to increase patient understanding, involvement in the consultation, and decision-making ³⁶.

Furthermore, another important issue not assessed in our studies, is the role of cross-cultural differences in information provision. Truth telling and honest disclosure of cancer information appears to remain controversial in some southern countries ³⁷⁻³⁹. Awareness of a cancer diagnosis or prognosis is associated with more anxiety and depression, and poorer physical, social and emotional HRQoL in those countries ⁴⁰⁻⁴². Future studies should pay more attention to the cultural background of the survivor to get insight into differences in the perceived levels of received information and satisfaction.

Personality and the perceived level of information received

Cancer survivors with a Type D personality (combined effect of negative affectivity and social inhibition) perceived to receive less information. There exists a strong positive relation between positive affect and memory ⁴³, while negative affect is associated with difficulties to access, obtain, and understand cancer information ⁴⁴. Individuals scoring high on neuroticism, a trait closely related to negative affectivity, might have a preference for information that reassures them ⁴⁵. Cancer related information might be judged as threatening by Type D cancer survivors and will probably be accompanied by the experience of more negative emotions. The experience of negative emotions requires energy and can distract attention and diminish concentration. The recall of received information could therefore be hindered. Also, individuals with a Type D personality tend to use a “disengagement coping strategy” which involves avoiding or denying threatening information, seeking distraction and distancing oneself from the stressor or related feelings ^{46, 47}. Even if the HCP gives a large amount of information, it might be possible that the passive coping style leads to inadequate information processing, whereby the relevant information will not be picked up. Furthermore, previous studies show that one aspect of social inhibition is feeling insecure and less competent when communicating with others ^{48, 49}. These feelings might result in more difficulties in communicating with the HCP and a lower willingness to ask questions during a consultation when information needs are not met. Type D cancer patients may

benefit from behavioural interventions that are aimed towards reducing maladaptive coping strategies such as withdrawal ⁵⁰. Such interventions should focus on the empowerment of Type D patients to increase their health control and to reduce negative emotions ⁵¹. Strategies targeting HCPs may focus on their facilitating behavior, since this has been associated with enhanced patient satisfaction in patients less confident in communicating with their HCP ⁵².

Information provision and patient reported outcomes

Health-related quality of life in TC survivors

In the past decade a growing number of studies have documented the high prevalence of short-term, long-term and late effects of cancer treatment. Up to now, most survivorship studies examining PROs have focused on survivors of common cancer types (e.g. breast, colorectal and prostate cancer). To date little is known about the long-term HRQoL among TC survivors. Our systematic review showed that TC survivors report severe impairments of HRQoL after treatment (surgery, radioactive iodine ablation, suppressive thyroid hormone therapy). However, the benefits of radioactive iodine ablation and suppressive hormone therapy are of uncertain benefit for low-risk TC survivors ⁵³⁻⁵⁷. These treatments have even been associated with harmful effects on bone metabolism and the cardiovascular system ⁵⁸. Therefore, it is important to consider a more conservative therapeutic approach for these patients ⁵⁹.

The results of our long-term survivorship study show that thyroid cancer survivors experience deteriorated HRQoL compared to a normative population and TC specific problems even 20 years after primary diagnosis. In this study we did not find a direct relation between primary treatment type and long-term HRQoL, although it seems that problems related to surgery (voice, throat/mouth and problems with scar) were more often present in the first years after diagnosis. The decreased HRQoL and high levels of fatigue in the first years after diagnosis could be caused by the high suppressing doses of levothyroxine, resulting in subclinical hyperthyroidism. When doses of levothyroxine are then lowered to restore euthyroidism, symptoms related to thyroid dysregulation were expected to disappear. However, the symptoms remained present. Therefore, a possible explanation for the decreased HRQoL might be that these lower doses of levothyroxine after the high suppressing doses might not be the optimal (pre-operative) level for the specific patient and in that case the symptoms are a result of the supplemental thyroid hormone treatment ⁶⁰. Furthermore, long-term exposure to excess thyroid hormone can lead to (irreversible) changes of the autonomous nervous system, which could not be reversed by restoration of euthyroidism ⁶¹. These changes possibly influence the well-being of a patient and might also be an explanation for the symptoms patients experience even long-term after diagnosis. More research is needed into the exact mechanisms leading to the decreased HRQoL among TC survivors.

Despite the experience of these symptoms, patients are sometimes advised by HCPs that

TC is not a serious problem, partly as a consequence of the good prognosis for papillary and follicular TC ⁶². This attitude trivializes the importance of the disease and causes patients to feel dismissed as not having a serious disease ⁶³. The THYCA-QoL questionnaire can be of value in the evaluation of treatment effects and aftercare of TC survivors. It can make HCPs more aware of the potential HRQoL issues TC survivors are dealing with. HCPs can then provide TC survivors with information on (long-term) effects of TC and its treatment and care options and thereby possibly improve survivors' HRQoL.

Patient reported outcomes and information provision: chicken or egg causality dilemma

Results of this thesis show positive associations between information provision and patient reported outcomes (right part conceptual model; Figure 1). Especially satisfaction with the received information was strongly associated with better HRQoL, less anxiety, less depression and more positive illness perceptions. Nevertheless these results cannot be interpreted univocally, since the causal direction of the associations is not clear.

On the one hand, adequate information provision can lead to improved PROs. The pathways through which information can influence PROs might be direct or indirect. A lack of information or too much information can directly lead to anxiety, depression or a decreased HRQoL. The positive influence of information on PROs appears to be mostly indirect. Recent studies identified several indirect pathways through which information can lead to better PROs including increased access to care, greater patient knowledge and (shared) understanding, higher quality medical decisions, enhanced therapeutic collaboration, strengthened social support, patient empowerment, better management of emotions and coping, better sense of control, health competence and better symptom management and treatment adherence ⁶⁴⁻⁶⁷. With respect to the mental health component, information exchange can work therapeutic in that a HCP can express empathy which may help the patient to experience more positive emotions (hope, optimism and self-worth) instead of negative emotions (fear and anxiety) ^{68, 69 70}. An example for the physical health component could be that information provision about the beneficial effects of physical activity on treatment-related symptoms (e.g. fatigue) may help to motivate survivors to increase their physical activity levels and consequently diminish their symptoms.

On the other hand, it is possible that patients with higher levels of HRQoL and lower levels of distress naturally report higher levels of satisfaction with the received information, independent of the information they actually received. Furthermore, high levels of anxiety or depression and low HRQoL can inhibit information processing; patients with a poorer mental health may have more difficulty to understand the information even when the information is of high quality. A special group in this context are patients with advanced disease, who

might indicate to receive more information, but still have worse HRQoL and higher levels of anxiety and depressive symptoms as a consequence of their disease severity. For this group the message of information (with regard to prognosis) and the way the information is provided (empathy) are probably more important than the degree to which the information meets the informational needs ⁷¹. However, it is difficult for HCPs to remain optimistic while being honest about a poor prognosis ⁷².

Methodological considerations

The studies presented in this thesis are subject to various strengths and limitations. Several methodological issues have been highlighted in the previous chapters. In this section, some general limitations of the studies will be considered.

Study design

The studies included in this thesis, except for chapter 7, had a cross-sectional design. This limits the potential for drawing causal inferences. The causation may be reversed (e.g. chicken or the egg dilemma for information provision and PROs). Prospective studies can give more insight into changes over time, but are still limited in establishing causality. In addition, other characteristics may confound the relationship between the dependent and independent variables. Although we adjusted our analyses for potential confounders, some candidate confounders were lacking (e.g. cultural background, health literacy levels and biochemical data) and could not be taken into account.

Measurements

Clinical and physiological data and reference groups

Despite the rather clinical focus of the population-based Netherlands Cancer Registry, several important parameters were not registered for TC patients (e.g. extent of surgery, levothyroxine dose, applied treatments during follow-up, tumour size). Furthermore, information on biochemical parameters of TC (TSH levels and serum free T3 and T4) was lacking. Long-term assessment of biochemical and treatment parameters in combination with the assessment of TC specific HRQoL (THYCA-QoL) could give more insight into the mechanisms accounting for the decreased HRQoL among TC survivors. In addition, comparison of a group of TC survivors with a group of patients with subclinical hyperthyroidism without cancer could be helpful to test whether or not the symptoms survivors experience are TC specific or related to thyroid dysfunctioning in general.

Information provision: EORTC QLQ-INFO25

The majority of survivors participating in our studies can be described as long-term (>5 years after diagnosis) cancer survivors, who are often out of the acute phase of medical treatment

and decision making. The EORTC QLQ-INFO25 is not specifically designed for assessment of information provision among this group. The questionnaire has been validated among newly diagnosed cancer patients receiving primary treatment and patients with recurrent/metastatic disease starting a second line of treatment ¹. The mean time since diagnosis was 3 - 5 years in our studies, which could influence the recall effect of information received. Although the Cronbach's alpha of the scales were good in all of our studies, further research is needed to test the psychometric properties of this questionnaire among long-term cancer survivors.

Furthermore, the EORTC QLQ-INFO25 only assesses the information patients indicated to have received (self-report). Notwithstanding the fact that the perception of the patient is most important, comparing data on actual information provision with the subjective data from our questionnaire would be of additional value. Patients often forget a substantial amount of the information given because it is complex and emotionally charged.

In addition, the EORTC QLQ-INFO25 does not measure who provided the information, and when the information was provided exactly. It would be interesting to assess which aspects of information patients receive from their different HCPs (i.e. radiation oncologist, medical oncologist, oncology nurse, general practitioner), at what point during their disease trajectory they receive the information, and whether these aspects are associated with usefulness of and satisfaction with the information received.

Finally, since the EORTC QLQ-INFO25 is not a measure of clinical outcomes, it was not possible to determine clinical meaningful differences. Differences in the perceived receipt of information might be statistically significant yet considered as unimportant. In this respect, it would be interesting to study how patients define an important improvement/worsening of information provision. With this information HCPs could better interpret the importance of our research findings.

Future directions

Cancer survivorship studies show that many survivors, including survivors of rare tumours, like thyroid cancer, face continuing physical and psychosocial problems long after completion of primary treatment. Achieving and maintaining optimal well-being is an important objective of current cancer treatment and of cancer rehabilitation and aftercare. One of the most important aspects of cancer care is the provision of adequate information. Survivors who are satisfied with the received information report better PROs compared to survivors who are dissatisfied. However, several areas of information provision were experienced as insufficient. Therefore, future research should focus on strategies to improve the information provision. In this section we will discuss some strategies to improve information provision, for cancer survivors in general and TC survivors specifically.

Unraveling the information needs of cancer survivors

The perceptions of HCPs about patients' needs should become in agreement with the actual needs of the patient. The best way to unravel the information needs of a patient is to consult the patient, but this is rarely done and research is limited ⁷³. Also, a neglected aspect of a consultation is checking the understanding of the patient ⁷⁴. It is necessary to regularly check what the patient has understood ⁷⁵ and whether the information was helpful ⁷⁶. When necessary, the HCP must repeat the information several times, both between and within consultations ⁷⁷. Cancer patients may not always be able to retain and process information because they may be emotionally overwhelmed ^{78, 79}, impaired in their cognitive capability, or deny their illness as a coping strategy to retain hope ^{80, 81}. Therefore, the timing and the way information is provided are important factors to take into account. Furthermore, awareness of the background characteristics associated with the perceived receipt of information could help HCPs to provide more patient-centered information.

Decision aid for TC survivors

TC survivors perceive to receive conflicting recommendations on radioactive iodine treatment from their HCP ⁶³. Information on rationale, risks and uncertainties relating to this treatment are perceived as insufficient. Most of the times no treatment choice was offered and patients felt the treatment was imposed on them. Since there is uncertainty about the effectiveness of radioactive iodine treatment and TSH suppression for low-risk TC patients, informed decision making and patient involvement should be improved. A decision aid intended to be used as an adjunct to individualized HCP counseling proved to increase medical knowledge and informed medical decision making in patients with early-stage papillary TC who were considering adjuvant radioiodine treatment ^{82, 83, 84}. Other studies showed that the use of decision aids can enhance patient satisfaction and understanding without increasing anxiety, even in patients with advanced cancer ^{85, 86}.

Survivorship Care Plan

A recent communication strategy devised to address the information needs of cancer survivors is a Survivorship Care Plan (SCP) ^{27, 87}. Previous studies have shown that providing patients with written information increases their recall, knowledge and satisfaction with information ^{88, 89}, although general written information is often not empowering. A SCP provides cancer survivors with a summary of their course of treatment as a formal document ⁸⁷. Essential in such a SCP is detailed information provision about diagnosis and treatment of cancer, possible long-term and late effects and management thereof, lifestyle and cancer surveillance recommendations, and available resources ⁹⁰. The SCP is expected to be an empowering and enabling device ⁹¹, by facilitating better understanding and self-care by the patient. However, evidence concerning the effectivity of the SCP to improve PROs is lacking ⁹².

Feedback of PROs from patient to HCP

The most frequently reported unmet need among cancer survivors was information about long-term effects and aftercare. More than 60% of survivors report that their HCP lacked complete knowledge of how their HRQoL was affected by cancer and its treatment ⁹³. A way to focus on key topics during a consultation is feedback of PROs. Feedback on HRQoL information to HCPs has the potential to help detect unmet needs and symptoms leading to better control and monitoring of such issues, serve as a guide for HCPs to discuss HRQoL issues, act as patients' voice, and facilitate individualized information provision and care ⁹⁴. Research shows that PRO feedback to HCPs was effective in initiating discussion of problematic HRQoL and was able to focus the conversation on topics relevant for the patient without extending the visit ⁹⁵. However, another study showed that PRO feedback alone does not overcome the existing barriers that prevent HCPs from discussing HRQoL issues with their patients ⁹⁴.

Future studies should investigate whether feedback of PROs directly to the patient is more effective in initiating a discussion than feedback of PROs to the HCP alone. One way to give PRO feedback directly to the patient is by a web-based intervention. An increasing number of patients participating in our PRO studies fill in the questionnaires online ⁹⁶. When the raw online questionnaire data could be translated into easy interpretable graphical representations, this will give the patient insight into their own well-being compared to other cancer patients or a normative population. This PRO information may empower patients to initiate discussions about these topics with their HCP. The effectiveness of a web-based intervention, aimed at providing feedback on PROs directly to the patient, in increasing patient satisfaction with information and addressing unmet informational needs should be explored.

Concluding remarks

The number of cancer survivors is rapidly increasing in the Western world. The increasing incidence rates of TC can partially be explained by the improved diagnostics, possibly leading to overdiagnosis and accompanying overtreatment. Cancer survivors often experience a diminished HRQoL and higher levels of anxiety and depression as a result of cancer and its treatment. Recognition and monitoring (e.g. with the THYCA-QoL for TC survivors) of the specific health problems survivors' are dealing with is important to provide optimal supportive care. Another important aspect of survivorship care is information provision. Satisfaction with received information is related to better PROs. However, several areas of information provision are experienced as insufficient. The identification of specific information needs could facilitate a more patient-tailored approach of informing patients. Besides, HCPs need to be aware of the clinical and socio-demographic factors associated with these information needs and perceptions of received information. A more patient-tailored

approach of information provision may contribute to improved satisfaction levels and PROs in cancer survivors. Strategies to improve information provision to cancer survivors, like survivorship care plans and feedback of PROs directly to the patient, need to be explored.

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CHAPTER 14

Nederlandse samenvatting (Summary in Dutch)

Dankwoord (Acknowledgments)

List of publications

About the author



Nederlandse samenvatting (Summary in Dutch)



NEDERLANDSE SAMENVATTING (SUMMARY IN DUTCH)

Inleiding

Toenemend aantal (ex-)kankerpatiënten

Door de vergrijzing van de bevolking en het dalende risico om aan kanker te overlijden, dankzij steeds vroegere opsporing en verbeterde behandeling, neemt het aantal (ex-)kankerpatiënten fors toe: van 600.000 (ex-)patiënten in 2010 tot ongeveer 915.000 in 2020. Er wordt in toenemende mate onderzoek gedaan naar de late en langdurige effecten van kanker en de behandeling op het psychosociaal welbevinden van (ex-)kankerpatiënten. Studies tonen aan dat sommige (ex-)kankerpatiënten tot wel 15 jaar na diagnose nog een verminderde kwaliteit van leven hebben in vergelijking met een Nederlandse normpopulatie.

Zorg voor (ex-)kankerpatiënten

Informatievoorziening is een van de belangrijkste aspecten van de ondersteunende zorg voor (ex-)kankerpatiënten. Op basis van goede informatie kan een patiënt beter beslissingen nemen over de behandeling, worden de behandelprocedures beter opgevolgd en heeft de patiënt het idee meer controle te hebben over de situatie. Uit eerder onderzoek blijkt dat (ex-)patiënten vaak niet in hun informatiebehoefte worden voorzien en daardoor ontevreden kunnen zijn over de hoeveelheid ontvangen informatie. Informatie met betrekking tot de ziekte en behandeling is mogelijk van invloed op andere patiënt gerapporteerde uitkomstmaten zoals de kwaliteit van leven van (ex-)kankerpatiënten.

Schildklierkanker

Onderzoek naar het psychosociaal welbevinden heeft zich tot nu toe voornamelijk gericht op (ex-)kankerpatiënten met veelvoorkomende tumoren zoals prostaatkanker, borstkanker, longkanker en dikkedarmkanker. Er is nog relatief weinig bekend over de impact van kanker en de behandeling op de lange termijn kwaliteit van leven van (ex-)patiënten met minder vaak voorkomende tumoren zoals schildklierkanker. Elk jaar worden er 500-600 patiënten in Nederland gediagnosticeerd met schildklierkanker. Door de toenemende incidentie en goede prognose van de papillaire en folliculaire tumoren (5-jaarsoverleving >90%) neemt het aantal (ex-)schildklierkankerpatiënten snel toe.

De primaire behandeling van schildklierkanker bestaat meestal uit het (geheel of gedeeltelijk) operatief verwijderen van de schildklier. Patiënten krijgen na een totale verwijdering van de schildklier een behandeling met radioactief jodium. Wanneer de schildklier volledig verwijderd is worden er geen schildklierhormonen meer aangemaakt. Daarom moeten (ex-)patiënten de rest van hun leven schildklierhormonen slikken, in de eerste jaren vaak met een hoge dosis. Schildklierkanker kan na de behandeling terugkomen. Dit betekent dat (ex-)schildklierkankerpatiënten ook regelmatig gecontroleerd moeten worden. Gezien de goede

prognose en de agressieve behandeling is het van groot belang te weten wat de effecten van schildklierkanker en de behandeling ervan zijn op de (lange termijn) kwaliteit van leven. Met dit inzicht kan de (na)zorg aangepast worden aan de behoeftes van (ex-)patiënten.

Doel van dit proefschrift

Het doel van dit proefschrift was tweeledig. In deel I is getracht een beeld te krijgen van de hoeveelheid ontvangen informatie en tevredenheid daarmee bij verschillende groepen (ex-)kankerpatiënten in verschillende fasen van hun ziekte. De invloed van de hoeveelheid ontvangen informatie en de tevredenheid daarmee is vervolgens gerelateerd aan kwaliteit van leven, niveaus van angst en depressie. In deel II is de focus gelegd op de (lange termijn) kwaliteit van leven van (ex-)schildklierkankerpatiënten.

Voornaamste bevindingen van het proefschrift

Deel I: Informatievoorziening en patiënt gerapporteerde uitkomstmaten

In **hoofdstuk 2** werd de hoeveelheid ontvangen informatie en de tevredenheid daarmee onder (ex-)melanoompatiënten in kaart gebracht. Van de (ex-)melanoompatiënten gaf 9 tot 37 procent aan geen informatie te hebben ontvangen over verschillende aspecten van de ziekte en diagnose, terwijl 38 procent van deze patiënten rapporteerde geen informatie te hebben gehad over de behandeling. Met betrekking tot de nazorg en follow-up gaf 84 tot 94 procent van de patiënten aan geen informatie te hebben gehad. Meer dan de helft van de (ex-)melanoompatiënten (61 procent) was niet tevreden met de hoeveelheid ontvangen informatie. Daarnaast gaf een kwart van de patiënten aan graag meer informatie te willen ontvangen van hun behandelend arts.

Verder liet dit onderzoek ook zien dat patiënten met een hoog ziektestadium, hoog opleidingsniveau en jonge leeftijd bij diagnose aangaven meer informatie te hebben ontvangen van hun arts in vergelijking met patiënten met een laag ziektestadium, lager opleidingsniveau en hogere leeftijd ten tijde van de diagnose. Verder waren hoger opgeleiden en patiënten die gebruik maakten van het internet meer tevreden met de ontvangen informatie ten opzichte van lager opgeleiden en patiënten die geen gebruik maakten van internet. Een ander belangrijk punt was dat de tevredenheid over de ontvangen informatie sterk verschilde per ziekenhuis van diagnose en behandeling.

Naast relaties tussen informatievoorziening en klinische en demografische factoren, kunnen psychologische factoren zoals persoonlijkheid ook gerelateerd zijn aan de hoeveelheid ontvangen informatie en de tevredenheid daarmee. In **hoofdstuk 3** werd daarom de relatie onderzocht tussen Type D persoonlijkheid en informatievoorziening bij 3080 (ex-)kankerpatiënten. Iemand met een Type D persoonlijkheid heeft een combinatie van twee persoonlijkheidskenmerken: negatieve affectiviteit (de neiging om negatieve emoties te

ervaren) en sociale inhibitie (de neiging om jezelf of je emoties niet te uiten in het bijzijn van anderen). Patiënten met een Type D persoonlijkheid gaven aan minder informatie te hebben ontvangen, minder tevreden te zijn met de ontvangen informatie en de informatie ook minder bruikbaar te vinden in vergelijking met (ex-)patiënten zonder Type D persoonlijkheid. Deze resultaten werden ook gevonden na correctie voor klinische en socio-demografische factoren.

In **hoofdstuk 4** werd er door middel van systematisch literatuuronderzoek gekeken naar de relatie tussen enerzijds informatievoorziening aan patiënten en anderzijds kwaliteit van leven, niveaus van angst en depressie onder (ex-)kankerpatiënten. Het literatuuronderzoek werd uitgevoerd op basis van wetenschappelijke publicaties die tot februari 2010 verschenen op PubMed. Vijfentwintig artikelen, alle geschreven tussen 1996 en 2009, die voldeden aan de vooraf gedefinieerde inclusiecriteria, werden beoordeeld op basis van een lijst met kwaliteitscriteria. Daaruit kwam naar voren dat tevreden patiënten, patiënten die zich voldaan voelden ten aanzien van hun informatievoorziening, en patiënten die geen belemmeringen hadden bij het verzamelen van informatie over het algemeen een betere kwaliteit van leven rapporteren en minder last hebben van angstige en depressieve gevoelens. Van de acht studies die gericht waren op interventies ter verbetering van de informatieverstrekking aan patiënten, bleek slechts één studie een positief verband te vinden tussen informatievoorziening en kwaliteit van leven.

Uit eerder onderzoek is gebleken dat de ideeën en gedachten die patiënten hebben over hun ziekte (ziekteperceptie) sterk samenhangen met hun ervaren kwaliteit van leven. Mogelijk is er ook een relatie tussen ziekteperceptie en informatievoorziening, dit werd onderzocht in **hoofdstuk 5**. De resultaten lieten zien dat onder 3080 (ex-)patiënten (baarmoederkanker, dikkedarmkanker, lymfeklierkanker of multipel myeloom) de perceptie meer informatie over de ziekte te hebben ontvangen gerelateerd was aan een positievere ziekteperceptie van de kankerpatiënt (meer controle en beter begrip). Echter, de perceptie meer informatie te hebben ontvangen over nazorg was gerelateerd aan negatievere ziektepercepties (meer consequenties en symptomen toegeschreven aan de ziekte, ziekte van langere duur, minder controle van de behandeling, minder begrip en sterkere emotionele reactie op ziekte). (Ex-)kankerpatiënten die tevreden waren over de informatie die zij kregen, rapporteerden minder klachten en negatieve gevolgen die ze toeschreven aan kanker, rapporteerden het gevoel te hebben dat de behandeling controle had over de ziekte en dat de kanker van kortere duur was, gaven aan minder emotionele problemen en minder zorgen te hebben naar aanleiding van de ziekte en hadden een beter begrip van hun ziekte in vergelijking met ontevreden (ex-)kankerpatiënten.

In **hoofdstuk 6** werden de relaties onderzocht tussen informatievoorziening en patiënt gerapporteerde uitkomstmaten (ziekteperceptie, kwaliteit van leven, angst en depressie) onder patiënten met uitgezaaide dikkedarmkanker. Uit deze studie bleek dat de

informatievoorziening aan deze patiënten vergelijkbaar was met dikkedarmkankerpatiënten zonder uitzaaiingen. Patiënten met gemetastaseerde ziekte gaven echter wel aan meer informatie te hebben ontvangen over hun behandeling en meer informatie te willen hebben over het ziekteverloop en nazorg. Slechts 60% van de patiënten met uitzaaiingen was tevreden met de hoeveelheid ontvangen informatie. Het ontvangen van meer informatie over de ziekte en nazorg hing samen met slechter functioneren, meer depressieve klachten en minder begrip van de ziekte. Terwijl het krijgen van meer behandelinformatie samenhing met minder depressieve klachten en een beter begrip van de ziekte. Tevredenheid met de hoeveelheid ontvangen informatie was niet gerelateerd aan andere patiënt gerapporteerde uitkomstmaten.

De meeste studies beschreven in het literatuuronderzoek van hoofdstuk 4 hadden een cross-sectioneel studie design. Daarom werd de relatie tussen informatievoorziening en kwaliteit van leven, gevoelens van angst en depressie in **hoofdstuk 7** longitudinaal onderzocht (twee meetmomenten met een tussenliggende periode van twee jaar) onder lymfoom en multipel myeloom patiënten. De hoeveelheid ontvangen informatie verminderde licht over tijd (en het meest onder korte termijn overlevenden), terwijl kwaliteit van leven en depressieve of angstige gevoelens gelijk bleven over de twee meetmomenten. Tevredenheid met de hoeveelheid ontvangen informatie op het eerste meetmoment voorspelde kwaliteit van leven twee jaar later, echter na correctie voor kwaliteit van leven op het eerste meetmoment verdween de gevonden relatie grotendeels. Tevredenheid met de hoeveelheid ontvangen informatie op beide meetmomenten was gerelateerd aan betere mentale kwaliteit van leven in vergelijking met veranderende tevredenheid of ontevredenheid met de informatie.

Deel II: (Ex-)schildklierkankerpatiënten: een onderbelichte groep

Omdat er nog relatief weinig bekend was over patiënt gerapporteerde uitkomstmaten onder (ex-)schildklierkankerpatiënten, lag de focus van deel II van dit proefschrift op de (lange termijn) kwaliteit van leven van deze (ex-)patiëntgroep. In **hoofdstuk 8** werden trends in incidentie, prognose en sterfte van schildklierkanker tussen 1989-2009 in Nederland beschreven. Vanaf 1989 is de incidentie van schildklierkanker significant gestegen in Nederland, terwijl de sterfte is afgenomen. De prognose (5-jaars relatieve overleving) is gelijk gebleven behalve voor (verder) gevorderde tumoren waarvan de incidentie is afgenomen. Door de toegenomen incidentie en goede prognose van gedifferentieerd schildkliercarcinoom, neemt de prevalentie ook toe. De resultaten van dit hoofdstuk waren reden om de lange termijn kwaliteit van leven van (ex-)schildklierkankerpatiënten verder te onderzoeken.

In **hoofdstuk 9** werd de literatuur met betrekking tot de kwaliteit van leven van schildklierkankerpatiënten systematisch doorzocht. Het literatuuronderzoek toonde aan dat het ondergaan van een operatie (gehele of gedeeltelijke verwijdering van de schildklier) een

direct korte termijn negatief effect heeft op de kwaliteit van leven. Naarmate de tijd verstrijkt, keert de kwaliteit van leven weer terug naar het niveau van voor de operatie. Het slikken van schildklierhormoon (levothyroxine) kan leiden tot hyperthyreoïdie. Wanneer de patiënt moet stoppen met het slikken van schildklierhormoon voor radioactieve jodiumablatie of een nacontrole, leidt dit tot hypothyreoïdie, waardoor de kwaliteit van leven ernstig wordt aangetast. Het gebruik van recombinant humaan schildklierstimulerend hormoon (rhTSH) zorgt ervoor dat een patiënt door kan gaan met het slikken van schildklierhormoon, waardoor de kwaliteit van leven gehandhaafd blijft. Studies die hebben gekeken naar de kwaliteit van leven van de lange termijn overlevenden van schildklierkanker lieten tegenstrijdige resultaten zien, waardoor er over deze groep geen sterke conclusies getrokken konden worden. Het voornaamste probleem van de bestaande studies was het ontbreken van een valide vragenlijst om de schildklierkanker specifieke kwaliteit van leven te meten. Dat heeft er toe geleid dat wij een schildklierkanker specifieke kwaliteit van leven lijst (THYCA-QoL) hebben ontwikkeld, beschreven in **hoofdstuk 10**. Relevante klachten werden geïdentificeerd door middel van literatuuronderzoek en een focusgroep. De lijst met klachten die daaruit naar voren kwam werd voorgelegd aan 6 artsen en 18 patiënten, die de klachten vervolgens beoordeelden op relevantie en de 25 belangrijkste klachten benoemden. Dit resulteerde in een lijst van 30 klachten die vervolgens in vragenformaat werden omgezet volgens de regels van de European Organisation for Research and Treatment of Cancer – Quality of Life Group. Het voortesten van de lijst onder 306 (ex-)schildklierkankerpatiënten leidde tot een uiteindelijke vragenlijst van 24 items en zeven conceptuele schalen (neuromusculaire, stem, concentratie, sympathische, keel/mond, psychologische en sensorische problemen).

De vragenlijst werd vervolgens gebruikt om de kwaliteit van leven van (ex-)schildklierkankerpatiënten in kaart te brengen (**hoofdstuk 11**). De kwaliteit van leven van patiënten die 2-20 jaar geleden de diagnose schildklierkanker kregen, bleek lager te zijn dan die van de gemiddelde Nederlander met dezelfde leeftijd. Zowel hun lichamelijke als mentale gezondheid bleek slechter. Naast een lagere kwaliteit van leven rapporteerden (ex-)schildklierkankerpatiënten ook meer klachten op het gebied van vermoeidheid, slapeloosheid, kortademigheid, gebrek aan eetlust en stofwisselingsklachten. Daarnaast rapporteerden (ex-)schildklierkankerpatiënten ook lange tijd na de primaire behandeling (>10 jaar) nog medische klachten zoals concentratieproblemen, hormonale problemen, psychologische problemen en plotseling invallende vermoeidheid. Vooral deze kankerspecifieke klachten verklaarden voor een groot deel (41-58%) de verminderde kwaliteit van leven van (ex-)schildklierkankerpatiënten in vergelijking met een controlegroep zonder kanker.

In het voorgaande hoofdstuk kwam vermoeidheid naar boven als een veelvoorkomende klacht onder (ex-)schildklierkankerpatiënten. Specifiek onderzoek naar de vermoeidheidsniveaus van (ex-)schildklierkankerpatiënten ontbrak, daarom werd er in **hoofdstuk 12** onderzocht wat de prevalentie van vermoeidheid is onder korte en lange termijn overlevenden van

schildklierkanker. De resultaten lieten zien dat 40% van de (ex-)schildklierkankerpatiënten hoge niveaus van vermoeidheid rapporteren. Zowel korte als lange termijn overlevenden rapporteerden hogere vermoeidheidsniveaus in vergelijking met de gemiddelde Nederlander met dezelfde leeftijd en geslacht. De verschillen waren alleen klinisch relevant voor lange termijn overlevenden in vergelijking met de normpopulatie. Schildklierkanker specifieke klachten (neuromusculaire, concentratie en psychologische klachten) en mentale gezondheid (angstige/depressieve klachten) waren het sterkst gerelateerd met vermoeidheid.

Concluderende opmerkingen

Het aantal (ex-)kankerpatiënten stijgt snel in de Westerse wereld. De toenemende incidentie van schildklierkanker kan deels worden toegeschreven aan verbeterde diagnostiek, mogelijk leidend tot overdiagnose en samengaannde overbehandeling.

(Ex-)kankerpatiënten ervaren vaak een verminderde kwaliteit van leven en hogere niveaus van angst en depressie als een gevolg van kanker en de behandeling. Herkenning en monitoren van de specifieke klachten waar (ex-)kankerpatiënten mee te maken krijgen (bijvoorbeeld door middel van afname van ziektespecifieke vragenlijsten) is belangrijk om optimale nazorg te kunnen bieden. Een ander belangrijk onderdeel van zorg voor overlevenden van kanker is informatievoorziening. Tevredenheid met de hoeveelheid ontvangen informatie is gerelateerd aan betere patiënt gerapporteerde uitkomstmaten. Echter, verschillende aspecten van de informatievoorziening worden nu nog als onvoldoende ervaren. Het achterhalen van de specifieke informatiebehoeftes van de (ex-)patiënt kan bijdragen aan een patiëntgerichte benadering. Daarnaast moeten zorgverleners zich bewust zijn van de klinische en socio-demografische factoren die samenhangen met de informatiebehoefte en de perceptie van de hoeveelheid ontvangen informatie. Een meer patiëntgerichte benadering zal mogelijk bijdragen aan verbetering van de tevredenheid van de patiënt en andere meer positieve patiënt gerapporteerde uitkomstmaten. De effectiviteit van strategieën om de informatievoorziening te verbeteren, zoals individuele zorgplannen en/of terugkoppeling van patiënt gerapporteerde uitkomstmaten aan de patiënten zelf (in plaats van aan alleen de zorgverlener), moeten verder worden onderzocht.

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List of publications



LIST OF PUBLICATIONS

Manuscripts included in thesis:

Husson O, Denollet J, Oerlemans S, Mols F. Satisfaction with information provision in cancer patients and the moderating effect of Type D personality. *Revision submitted*.

Husson O, Haak HR, van Steenbergen LN, Nieuwlaat WA, van Dijk BAC, Nieuwenhuijzen GAP, Karim-Kos H, Kuijpers J, van de Poll-Franse LV, Coebergh JW. Rising incidence, no change in survival and decreasing mortality from thyroid cancer in The Netherlands since 1989. *Revision submitted*.

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Olga Husson was born on October 19, 1984 in Breda, The Netherlands. After she graduated from high school at the Prisma Graaf Engelbrecht in Breda she obtained her Bachelor's degree in Human Movement Sciences at VU University Amsterdam. Subsequently, she followed the master Human Movement Sciences with a specialization in Sport Psychology at the same institution, which she completed cum laude in August 2007. After working as a junior researcher at Erasmus University Rotterdam, department of Child and Adolescent Psychiatry, she started her PhD project at Tilburg University in March 2009. Her research focused on information provision and patient reported outcomes among cancer survivors. During her PhD research she studied Epidemiology at VU University Amsterdam and obtained the Basic Teaching Qualification at Tilburg University in December 2012.

